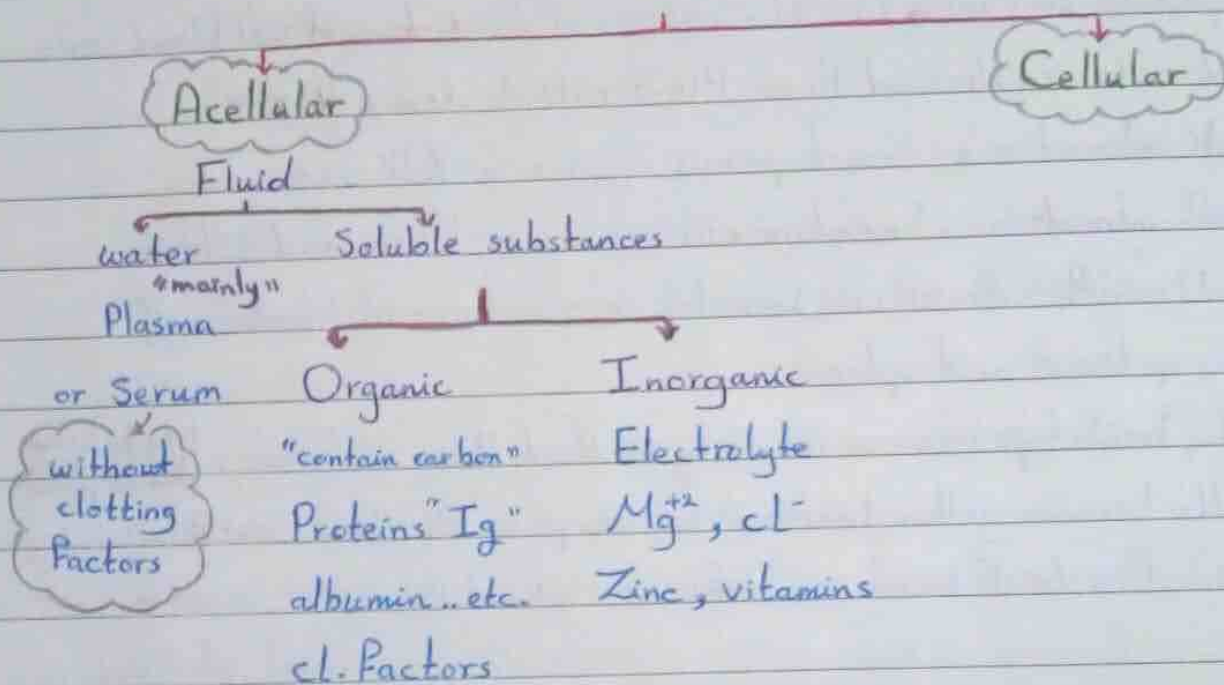


Hematology

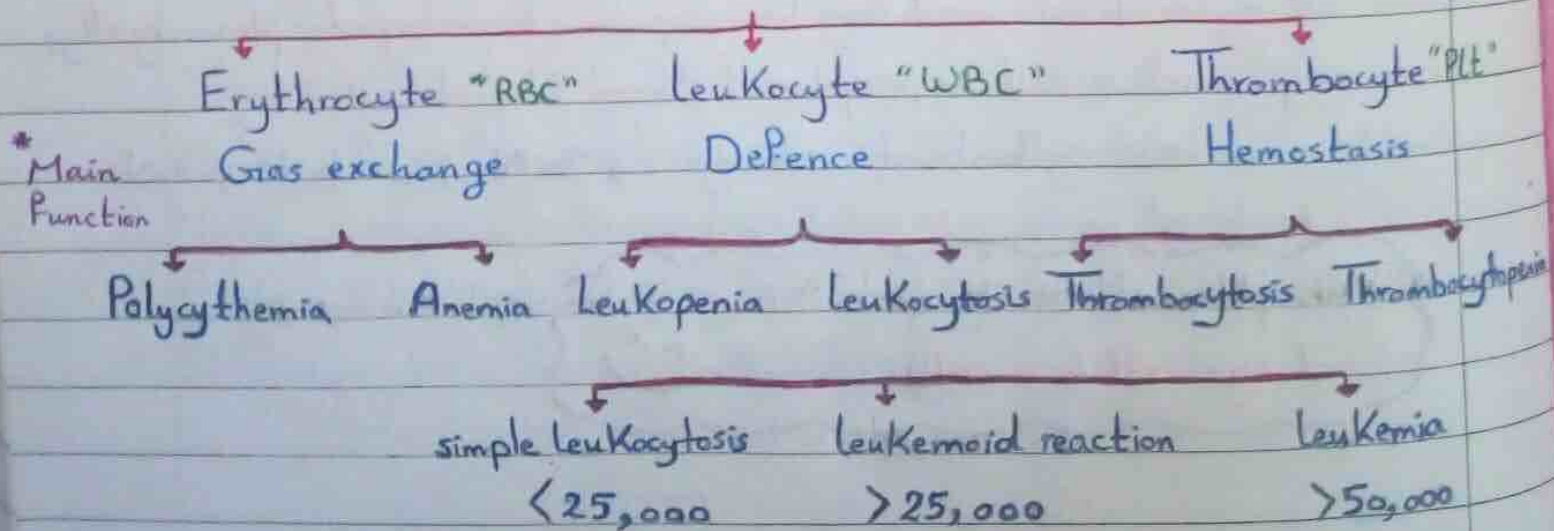
Principles of Hematology :-

- **Homeostasis** :- state of steady internal conditions maintained by living things.
- **Hemostasis** :- Process which causes bleeding to stop.

Elements of Blood



Cellular part



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C/P of patient with Hematological problem :-

- ① Anemia ② Recurrent infection ③ Bleeding

* The gold standard way for Dx hematological problems is investigation or Data interpretation; Because all hematological diseases sharing the same symptoms.

Note $\Rightarrow$ complete Blood count = Full blood count = Blood picture
(CBC) (FBC)

Hematopoiesis :- Def $\Rightarrow$ It's the process of Formation of all blood cells.

All blood cells are derived from Pluri potent stem cell.

- * 3rd week intrauterine, hematopoiesis occurs in Yolk sac.
 - * 3rd Month intrauterine, hematopoiesis occurs in Liver and spleen.
 - * End of 4 month intrauterine, hematopoiesis occurs in Medulla of all bones + liver and spleen.
 - * By birth, hematopoiesis occurs only in Red Bone marrow. Medullary Hematopoiesis
- In adults become yellow bone marrow, except in Flat bones ex: Pelvis and proximal ends of humeri and femori $\rightarrow$ Red Bone.

Note $\Rightarrow$ Ineffective BM $\rightarrow$ Extra medullary hematopoiesis.

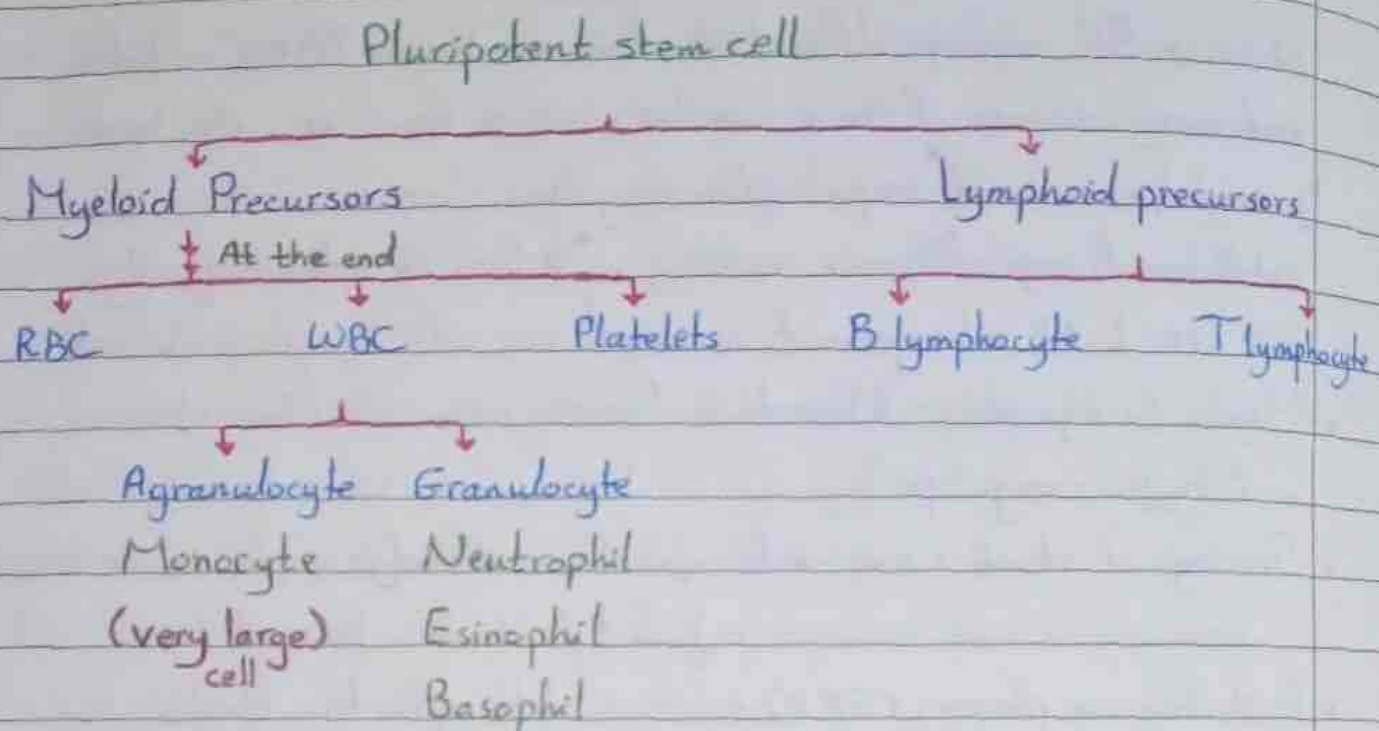
and all cases of extra medullary hematopoiesis have hepatosplenomegally, releasing immature cells in peripheral Blood (blast cells)

$\Rightarrow$ Massive leukoerythroblastic changes $\rightarrow$ B.M $\rightarrow$ $\rightarrow$ $\rightarrow$

Young age cell is large in size

Old age cell is small in size





Platelets derived From Megakaryocyte.

Megakaryocyte produce also Platelet GF For Fibrosis.*

- Non Functional**
- Cancer is division of cells not under control of human physiology
 - * Acute leukemia characterized by ↑ immature cells (Blast) with acute onset and rapidly dying.
 - * Chronic leukemia characterized by ↑ mature cells (cyte) due to failure of apoptosis.

Types of proliferation = Malignancy

Myeloproliferative

1. ↑ RBC → Polycythemia rubra vera.
2. ↑ WBC → Myeloid leukemia (CML)
3. ↑ PLT → Essential thrombocytosis.
4. ↑ Megakaryocytes + Fibrosis → Myelofibrosis.

Lymphoproliferative

1. Lymphoma → Hodgkin & non Hodgkin.
2. Lymphoid leukemia (CLL)
3. Multiple myeloma

Notes $\Rightarrow$ All myeloproliferative diseases have JAK2 mutation and every disease of them can be change to other. also have

* pancytopenia and hepatosplenomegally.

CML and myelofibrosis causing $\rightarrow$ * Massive splenomegally will less L.N enlargement in comparison with Lymphoproliferative.

* Myelo & Lymphoproliferative diseases are risky for stasis and hypercoagulopathy.

* Serological studies evaluate specific antibody in plasma or serum.

Antibodies لا تُعزل

* Fresh Frozen plasma (FFP) contain clotting factors, that's why it's given to Bleeding tendency cases.

The most important 3 hematological investigation are:-

① CBC

② Blood Film

③ B.M

During General examination, important to do exposure for iliac crest site $\rightarrow$ if there's plaster think of Aplasia or malignancy.

* Mechanism of polycythemia either by :-

- Hypoxemia $\rightarrow$ $\uparrow$ erythropoietin From Kidneys $\rightarrow$ $\oplus$ B.M For RBC's synthesis.
So any chronic hypoxemia due to "smoking, lung problem...etc" can results to 2^{ry} Polycythemia.

While 1^{ry} "idiopathic" polycythemia $\rightarrow$ Polycythemia rubra vera due to mutation in B.M "cancer".

* We can differentiate between 1^{ry} & 2^{ry} polycythemia by Erythropoietin level $\rightarrow$ High $\rightarrow$ 2^{ry}.

$\rightarrow$ low or undetected $\rightarrow$ 1^{ry}.

- * Leukemoid reaction occurs due to Severe infection, severe burn or severe trauma. ex:- EBV infection $\rightarrow$ WBC can reach 30,000 but it's well functional (leukocyte Alkaline phosphatase is high).
- if the leukocyte ALP is low $\rightarrow$ WBC is non functional and think of leukemia.
- * Not all cases of thrombocytosis can lead to thrombosis.
Functional platelets only, and Rx by aspirin.
while non functional lead to Bleeding.
- * Jak2 mutation can be congenital or acquired from carcinogenic substances.
- * Platelets $> 450,000/\mu\text{l}$ $\rightarrow$ Thrombocytosis
- * Platelets $> 1,000,000/\mu\text{l}$ $\rightarrow$ Cancer "Essential thrombocytosis" mostly.
but cancer can be presented also if plt count $< 1,000,000/\mu\text{l}$.
- * The Rx of all types of myeloproliferative diseases is Hydroxyurea because have the same origin $\rightarrow$ JAK2 mutation.
- * All Lymphoproliferative diseases affecting B-lymphocyte more than T-lymphocyte.
- * B-lymphocytic cancer is better prognosis than T-type $\rightarrow$ poor prognosis
All Hodgkin Lymphoma derived from B-lymphocyte, so it's better prognosis.
There's L-N enlargement in Lymphoproliferative diseases with less Organomegally.
- * Bone marrow Failure in acute leukemia occurs "early" Because blast cells multiplying inside the B.M ($\uparrow$ N. of non functional WBC) & interfere with RBC's and PLT release from the B.M ($\downarrow$ PLT, $\downarrow$ RBC's)
 $\rightarrow$ Anemia, Bleeding, Recurrent infection. $\rightarrow$ من جهة الخلايا

While in chronic leukemia, The cells multiplying in periphery first and causing hepatosplenomegally then $\rightarrow$ B.M Failure "Late"

Erythropoiesis:- Myeloblast

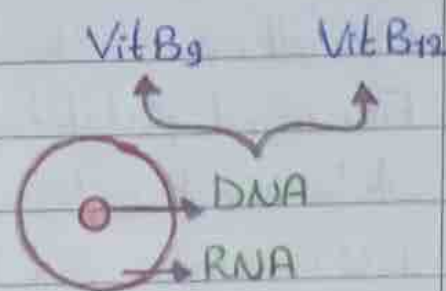
$\downarrow$
Proerythroblast

$\downarrow$
Erythroblast

$\downarrow$
Normoblast

(B.M)
 $\downarrow$
Peripheral Blood

Reticulocyte $\rightsquigarrow$ RBC 98%
1.2 - 2%



- * Vit B9 and Vit B12 important for DNA replication. Absence of Vit B9 and Vit B12 lead to ~~Nuclear~~ maturational arrest. but cytoplasm will replicate without division $\rightarrow$ blast, large cell and hypersegmented called $\rightarrow$ Megaloblastic cell.
- In peripheral blood find $\rightarrow$ Macrocytosis, ovale in shape. & in severe cases maybe find Megaloblastic cell in peripheral Blood $\rightarrow$ which's diagnostic for Megaloblastic anemia.
- * Alcohol, Hypothyroidism and pregnancy $\rightarrow$ slow rate of DNA division & release $\rightarrow$ Macrocytic non Megaloblastic.
- * Megaloblastic anemia starting with anemia and ended by pancytopenia. (Late)

D/D of pancytopenia :- ① Hypersplenism, ② B.M Failure
③ Aplastic anemia ④ Megaloblastic anemia.

- * In anemia maybe find false reticulocytosis, but the absolute Number of RBC is normal.

Absolute number more accurate the percentage % of Reticulocytes because percentage is affected by total Number of RBC's.

- * Presence of Reticulocytes in peripheral Blood indicate Functional Bone marrow. if reticulocytes is 0 $\rightarrow$ Aplasia.

- Step of conversion of Normoblast $\rightarrow$ Reticulocyte need iron, if there's iron deficiency $\rightarrow$ hypercellular B.M Full with Normoblast "as a predominant cell" and cytoplasm Full with protoporphyrin $\rightarrow$ Heme $\rightarrow$ $\text{Heme} = \text{Iron} + \text{Protoporphyrin}$

- * The 1st successful sign after treatment of iron deficiency anemia (IDA) is $\uparrow$ in reticulocyte count.

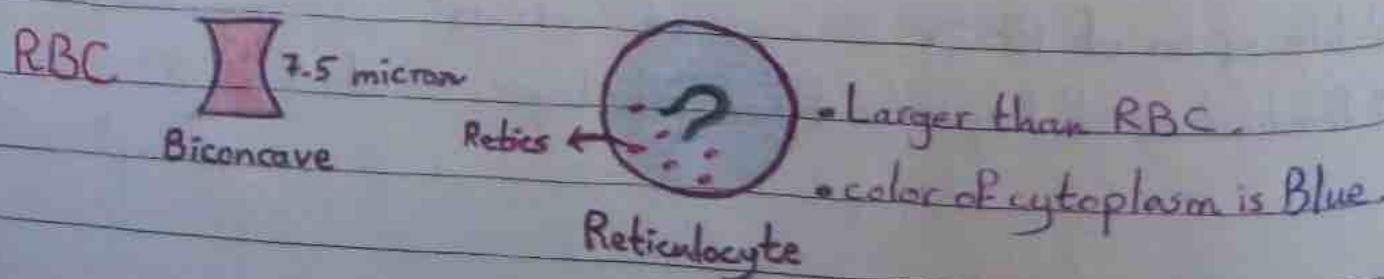
- * after 1 week of iron deficiency anemia Rx, if the reticulocyte not $\uparrow$ search for another cause of deficiency.

D/D of $\downarrow$ Reticulocytes :- ① Nutritional def. anemia "iron or B9 or B12"
② Aplastic anemia.

D/D of Reticulocytosis :- ① IDA on Rx.

② Megaloblastic anemia on Rx.

③ Hemolysis.

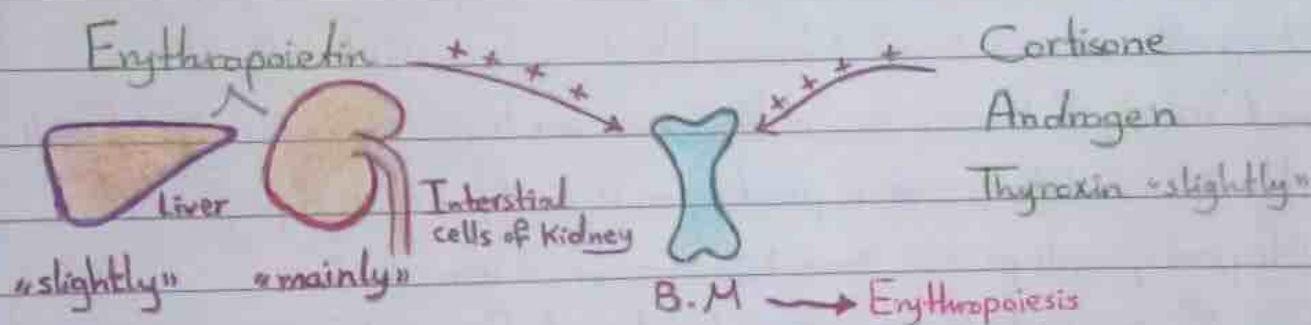


- * Any patient with reticulocytosis could have $\rightarrow$ Pseudo macrocytosis.
So one of the causes of macrocytosis in CBC is patient on reticulocytosis «as patient on Rx of IDA».

when there's reticulocytosis $\rightarrow$ There's anisocytosis

when there's reticulocytosis $\rightarrow$ There's Polychromasia

- * In iron deficiency anemia, The cell is microcytic hypochromic; because of drop in Hb $\rightarrow$ which's give the red color. and therefore the size of cell will be small. صغيرة وباهية 



- * Hb level in male $>$ Female due to Androgen.
- * $\downarrow$ in erythropoietin as in chronic Kidney disease, or patient have Adrenal insufficiency will results to Normocytic normochromic anemia. Because the size and color of RBC's are normal.
 $\downarrow$ in number of RBC's only.
- * Any chronic inflammation produce TNF α :-
 - ① $\downarrow$ Production of erythropoietin from the Kidney.
 - ② $\downarrow$ Sensitivity of B.M. to the erythropoietin.
 - ③ $\downarrow$ life span of RBC's. "Early destruction".
 - ④ $\uparrow$ Production of hepcidin from the Liver. "Late".

So anemia of chronic illness in early stage is normocytic normochromic anemia & in late stage is microcytic hypochromic.

Investigations in hematology:-

① Complete Blood count (CBC)

CBC Parameters

① Hemoglobin $\rightarrow$ Male = 13-17g, Female = 12-16g.

② RBC numbers $\rightarrow$ Male = max $\rightarrow$ 6.5, Female = maximum 5.3 million.

RBC Indices

① MCV $\rightarrow$ 76-96 FL (80-100) it's the mean volume of one cell.

$<80 \rightarrow$ Microcytic, $>100 \rightarrow$ Macrocytic, $>110 \rightarrow$ mostly is Megaloblastic but we have to confirm by B.M Aspiration.

② MCH $\rightarrow$ 27-32 pg. it's the amount of Hb per cell.

It's not affecting by cell size.

<27 pg $\rightarrow$ Hypochromic, $\geq 32 \rightarrow$ Hyperchromia. $\rightarrow$ Not present in medicine.

③ MCHC $\rightarrow$ 31-35% $\rightarrow$ تركيز الهيموجلوبين. it's the concentration of Hb in the red cell.

The MCHC is similar to MCH as it reflect defects in Hb synthesis but the MCH is more accurate.

$\uparrow$ MCHC in Hereditary spherocytosis disease.

④ HCT (PCV) $\rightarrow$ it's the volume of packed RBC's in 100 ml Blood.

* HCT affecting directly by volume of fluid.

$\uparrow$ volume $\rightarrow \uparrow$ HCT, $\downarrow$ volume $\rightarrow \downarrow$ HCT

So HCT isn't used as idea unless exclude dehydration and overhydration.

③ Platelets $\rightarrow$ 150,000 - 450,000 / microliter of Blood.

70,000 $\rightarrow$ safe for open heart surgery. but should be functional.

$< 50,000 \rightarrow$ Bleeding after mild trauma.

$< 20,000 \rightarrow$ Severe body Hemorrhage.

$< 10,000 \rightarrow$ Spontaneous cerebral Hemorrhage.

* How you can differentiate Between the bleeding 2^{ry} to platelets and clotting Factors?

By site of Bleeding, platelets causing subcutaneous bleeding "Purpura", while clotting factors causing internal Hge.

④ WBC $\rightarrow$ 4000 - 11,000

Differential leukocytic count :- Neutrophils $\rightarrow$ 60%

Lymphocyte $\rightarrow$ 20 - 30%

Basophils $\rightarrow$ 2%

Eosinophils $\rightarrow$ 4%

Monocyte $\rightarrow$ 8%

If someone have Total leukocytic count $\rightarrow$ 4,000, Neutrophil $\rightarrow$ 60%

& another one have Total leukocytic count $\rightarrow$ 10,000, Neutrophil $\rightarrow$ 60%

Both are different in their immunity. one have lower border of normal leukocytic count & the other have normal count.

* that's why the absolute number of WBC's is more accurate than percentage.

* Normal absolute number of neutrophils is 3,000.

Neutrophil is the first defensive line in immunity. and if $\downarrow$ by chemotherapy drugs ($< 3,000$) will causing neutropenic infection and fever. $\rightarrow$ * should stop chemotherapy drugs.

$< 2,500 \rightarrow$ Severe neutropenia

Normal absolute number of lymphocytes is 1200.

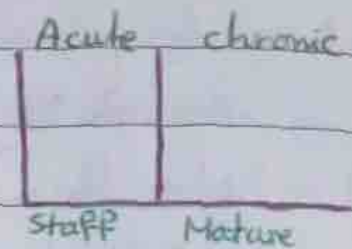
$< 1200 \rightarrow$ Lymphopenia.

During infection $\uparrow$ synthesis of immature WBC's "Staff cells".

$\rightarrow$ Curve dissociated to the Right.

During chronic infection as by T.B or chronic leukemia $\rightarrow \uparrow$ mature cells $\rightarrow$ Curve dissociated to the left.

Curve II يكون أعلى جمة اليسار.



⑤ Red cell distribution width (RDW)

Measure the variability of the size of RBC.

Normally is 7%, maximum 11-15%.

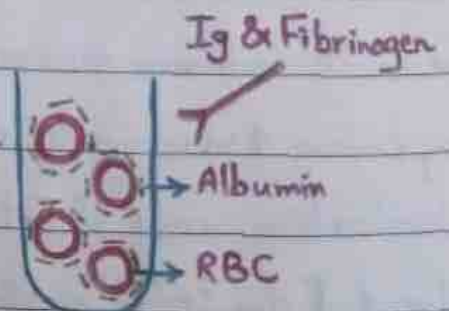
$\uparrow$ RDW occurs when there's large variability between cells.

$\uparrow$ Reticulocytosis $\rightarrow \uparrow$ RDW as in IDA on Rx and thalassemia.

Dimorphic anemia $\rightarrow$ Microcytic + Macrocytic cells at the same time (IDA + Folate deficiency) present & it's detected by blood film.

ESR $\rightarrow$ Blood cells sediment in a period of one hour normally more in adult female.

* Normally $\rightarrow \frac{\text{Age}}{2}$ ex: 70 yrs, ESR = 35.



* In Female $\frac{\text{Age}}{2} + 10$ ex: 70 yrs, ESR = 45.

* every 1g drop in Hb $\rightarrow \uparrow$ ESR 10mm.

ve charge prevent the precipitation.

Anemia $\downarrow$ RBC's $\rightarrow \uparrow$ precipitation $\rightarrow \uparrow$ ESR.

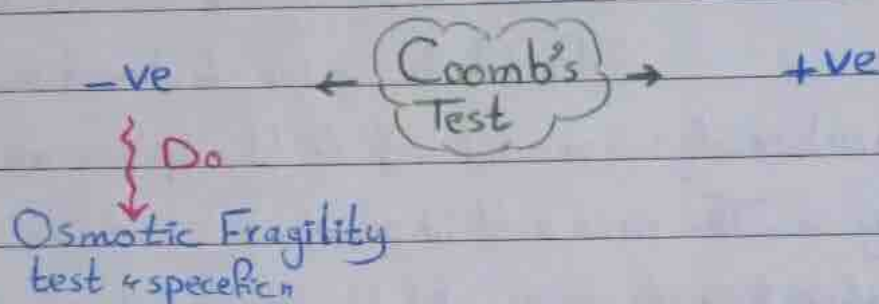
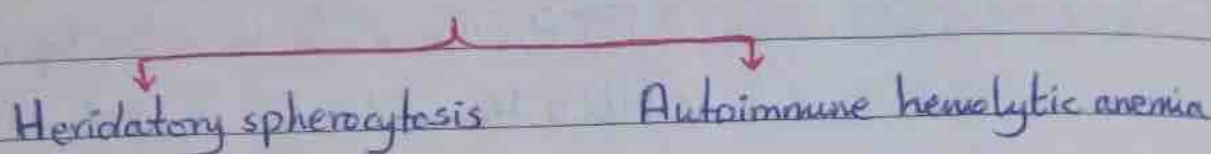
Polycythemia $\uparrow$ RBC's $\rightarrow \downarrow$ precipitation $\rightarrow \downarrow$ ESR.

- * $\uparrow$ Albumin $\rightarrow \uparrow$ -ve charge $\rightarrow \downarrow$ precipitation rate $\rightarrow \downarrow$ ESR.
- * $\downarrow$ Albumin as 2nd to $\downarrow$ P_{rt} intake, Malabsorption disease, Nephrotic syndrome, liver cirrhosis $\rightarrow$ All $\uparrow$ ESR.
- * Ig & Fibrinogen " $\uparrow$ in pregnancy and Hemorrhage" both are pro sedimentation agents $\rightarrow$ attached to some of RBCs & change it's charge to +ve $\rightarrow \uparrow$ Gravitation $\rightarrow \uparrow$ ESR.
- * So any infection $\uparrow$ Ig $\rightarrow \uparrow$ ESR. and Female around menses her ESR is higher than after menses.
- * Malignancy $\uparrow$ Antibodies $\rightarrow \uparrow$ ESR as Multiple myeloma (ESR > 100).
- * chronic infection as T.B $\rightarrow$ also (ESR > 100).
- * Giant cell arthritis "Polymyalgia rheumatica" $\rightarrow$ inflammatory process $\uparrow$ ESR.
- * So any infection, malignancy & inflammation $\rightarrow \uparrow$ ESR.
- * All types of anemia $\uparrow$ ESR except Hereditary spherocytosis and sickle cell anemia because have abnormal cell wall.
- * ESR > 100 ml/hr $\rightarrow$ Think of multiple myeloma, T.B, Giant cell arthritis when there's multifactorial factors as old age, H.F, anemia, UTI.
- * The most common cause of ESR > 100 is infection.
- * Any cause $\uparrow$ viscosity of Blood as polycythemia, Any cause of dehydration and Heart Failure $\rightarrow$ All will $\uparrow$ ESR.
- * Blood Film :- It's the examination of blood cells under the microscope by using very thin slide.
- * we look for $\Rightarrow$ shape, size, color, counting manually By specific slide

نقد ونظير الطول X العرض



- * Blood Film can detect Anisocytosis (variation in RBC size) and poikilocytosis (Abnormal RBC shapes) and Polychromasia (variation in RBC color).
 - * And can detect infectious diseases as malaria and malignant cell type "Blast or cyte" But B.M is more accurate.
- shape of RBC in Blood Film is normally Biconcave.
But could be $\Rightarrow$ Spherical RBC  "rounded"



 Sick cell RBC $\rightarrow$ Sick cell anemia or crisis.

 Ovale cell RBC $\rightarrow$ Hereditary erythrocytosis or macrocytic megaloblastic "2nd to Folate deficiency or Vit B₁₂ deficiency"



IF there's no destruction $\rightarrow$ RBC Full with remnant of DNA called $\rightarrow$ Howell jell body.

D/D of Howell-Jelly body in Blood Film :-

- 1 * Hypersplenism, either by autosplenectomy by diseases as sickle cell anemia or splenectomy or celiac disease.
- 2 * Megaloblastic anemia, due to $\downarrow$ vit B₉ & B₁₂ $\rightarrow$ megaloblastic cells inside & outside B.M $\rightarrow$ B.M can't destruct all these cells.

 Schistocyte RBC $\rightarrow$ in intravascular hemolysis diseases :-

- ① TTP "Thrombotic thrombocytopenic purpura".
- ② HUS "Hemolytic uremic syndrome".
- ③ DIC "Disseminated intravascular coagulation".
- ④ Prosthetic valve destruction.

* Extravascular hemolysis occurs inside the spleen and once do splenectomy $\rightarrow$ The case will improve.

But intravascular hemolysis $\rightarrow$ Not improve by splenectomy.

 Tear drop RBC $\rightarrow$ in Myelofibrosis disease, Formed by B.M
 B.M يبيك على الوقت في يشوف فيه Liver & spleen يمتلوا وعضولا
 Myelofibrosis disease is characterized by Hepatosplenomegally and Dry tap aspiration.

* B.M Examination :-

- $\rightarrow$ B.M Aspiration
- $\rightarrow$ B.M Biopsy (More accurate)

- ① Fat/cells ratio $\rightarrow$ $\uparrow$ in Aplasia.
 Normally cells/Fat ratio is more.

② Cellular population → Hypercellular
→ Normal
→ Hypocellular

Hypercellular $\rightarrow$ There's either peripheral destruction or malignancy.
• Hypercellular in form of malignant cell or hypercellular with compensation by normal cells.

IP hypocellular look for Fat/cells ratio to Dx Aplasia.

* How to differentiate between pancytopenia due to B-M Failure or due to peripheral destruction?

→ *look for Reticulocyte $\rightarrow$ if $= 0 \rightarrow$ most probably "Aplasia"

→ Do B.M biopsy to confirm

* Pancytopenia occurs either due to B-M Failure or Hypersplenism as in case of Long standing Rheumatoid arthritis (has joint deformities + pancytopenia due to hypersplenism) $\Rightarrow$ called "Felt's syndrome".

* How to differentiate between hypersplenism and B.M Failure due to cytotoxic drugs in Rheumatoid arthritis case?

* By injection of radioactive RBC $\rightarrow$ if appear flow inside the artery but not flow inside the vein $\rightarrow$ means there's hemolysis in the spleen $\rightarrow$ Hypersplenism

* IP patient have pancytopenia + Normal spleen + Reticulocyte in B.M $\rightarrow$ examine megaloblastic cells inside the B.M, because $\downarrow$ of vit₉ & vit B₁₂ early $\downarrow$ rate of production but not lead to 0 "zero" reticulocyte. and At the end lead to pancytopenia.

Thrombocytopenia is not C/I "contraindicated" For B.M Biopsy or aspiration, But you have to give Platelets transfusion before the procedure. "invasive procedure is risky for bleeding".

Anemia ...

Def:- It's a drop in oxygen carrying capacity below the expected regarding to age and sex after exclusion of overhydration.

Case 1 $\rightarrow$ his Hb is 9 & have severe symptoms.

Case 2 $\rightarrow$ " " " 6 & Asymptomatic.

From 2 previous cases, we conclude anemia symptoms doesn't depends on severity of Hb drop, but depends on the etiology.*

Even the level of Hb is low, patient can be asymptomatic if dropped gradually over time.

Case $\Rightarrow$ patient Hb = 4, but he's asymptomatic, not dyspnoic no headache, no Fatigue ...etc. what's the next step?

$\Rightarrow$ Repeat CBC test. **

* **Symptoms of anemia :- (And mechanism).**

1. when Number of RBC & Hb $\downarrow \rightarrow$ Tissue hypoxia $\rightarrow$ loss of Bounded $O_2 \rightarrow \downarrow$ affinity of O_2 Hb. $\rightarrow \odot$

2. Vasoconstriction in muscle Blood supply $\rightarrow$ Fatigue, and in Skin Blood supply $\rightarrow$ cold pallor skin.

"early pallor occurs due to Vasoconstriction, then become due to $\downarrow$ in Hb".

Vasodilatation occurs in cerebral Blood vessels $\rightarrow$ $\uparrow$ intra cranial pressure "Pseudotumor cerebri" $\rightarrow$ chronic headache + projectile vomiting + Papilledema "Blurred vision".
There's also loss of concentration and Anterograde "recent" memory.

$\downarrow$ Vit B₁₂ $\rightarrow$ * Mudness.

3. The heart is compensate by $\uparrow$ H.R "Tachycardia" which can precipitate H.F (High C.O type).

Chest pain and angina pectoris occur only in severe anemia.

Pulse $\rightarrow$ Large volume, collapsing (Hyperdynamic circulation).

$\downarrow$ O₂ supply to the Kidney will results to :-

[1] $\oplus$ RAS system $\rightarrow$ $\uparrow$ Na⁺-water retention $\rightarrow$ Volume overload.

[2] In severe cases $\rightarrow$ Pituitary anoxia $\rightarrow$ $\uparrow$ ADH "stress hormone"
 $\rightarrow$ $\uparrow$ H₂O reabsorption

[1] & [2] $\rightarrow$ Lead to Hypervolemia + compensated V.D +
 $\uparrow$ permeability of B.V $\rightarrow$ Edema without H.F.

* Dyspnea + Lower limb edema $\rightarrow$ Not always 2ry to Heart failure, especially if there's no orthopnea & paroxysmal nocturnal dyspnea.

- Symptoms and Signs (clinical pictures) :- "FOG P"

1. F $\rightarrow$ Fatigue, Fundoscopy. ^{ple Jais} Fatigue is Fixed constant without Diurnal or seasonal variation & Fundoscopy shows either papilledema or even retinal Hemorrhage in severe cases.

2. O $\rightarrow$ Oedema.

3. $G \Rightarrow$ General. $\downarrow$ concentration, $\downarrow$ memory, headache is ^{*}Bilateral occipital or temporal or over the eyes as Glaucoma.

Ejection systolic murmur as a sign, due to hyperdynamic circulation, or crepitation over the lung due to edema if patient precipitate Heart Failure.

* Mechanism of Dyspnea $\Rightarrow$ Hypoxemia $\downarrow$ $PaO_2 \rightarrow \oplus$ stimulate Respiratory drive $\rightarrow \oplus \uparrow$ R.R. "Tachypnea".

also congested lung by hyperdynamic circulation $\rightarrow \oplus$ stimulate Brain center
R.R $\uparrow \rightarrow$ Dyspnea especially with movement.

* characteristics of Dyspnea $\Rightarrow$ Gradual, progressive & Exertional. Similar as Dyspnea of Interstitial lung disease.

* GFR of the Kidney will $\uparrow$ due to $\uparrow$ volume & V.D, but the urine output is $\downarrow$ due to RAS system & ADH. " $\uparrow$ Reabsorption"

* $\uparrow$ Intestinal congestion (V.D) $\rightarrow$ Dyspepsia, anorexia, vomiting.

Anemia $\longleftrightarrow$ GIT disturbance

Causes of L.L edema in case of anemia (Bilateral):-

① Hypervolemia

② $\uparrow$ Permeability

③ Heart Failure $\rightarrow$ improve by elevation of legs.

if improved but still present, think of another cause in addition of H.F.

Edema could be 2ry to underlying cause (Disease) as Chronic Kidney disease (CKD) on top of Nephrotic syndrome.

Hypothyroidism, celiac disease both can cause edema and anemia. So important to ask during taking history which start first anemia or edema? to differentiate the edema is 2nd to anemia or due to underlying disease before starting of anemia.

To look for sign of anemia on palmar creases, should do Dorsiflexion.

Note $\Rightarrow$ Pallor conjunctiva appear below 10 g/dL.

Pallor palmar creases appear below 8 g/dL.

4. P $\Rightarrow$ Palpitation. $\rightarrow$ constant and continuous, $\uparrow$ more with activity.

* في المستوي لازم نقول الـ PT | خيطي على الطاولة

* Classification of anemia $\left\{ \begin{array}{l} \rightarrow \text{According to MCV \& MCH} \\ \text{(The best)} \\ \rightarrow \text{According to Etiology} \end{array} \right.$

↓	↓	↓
Nutritional	↓ Production	↑ loss
« ↓ vitamins or ↓ iron ».	« ineffective hematopoiesis or erythropoiesis from B.M »	« By Hemorrhage or Hemolysis ».

According to MCV & MCH

↓	↓	↓
MCV < 80 fL	MCV 80 - 100 fL	MCV > 100 fL
MCH < 27 Pg	MCH 27 - 32 Pg	MCH > 32 pg
(microcytic hypochromic)	(normocytic normochromic)	(macrocytic hyperchromic)

D/D of microcytic hypochromic anemia :-

1. Iron deficiency anemia → The most common anemia in all age groups except elderly.

2. Thalassemia.

3. Sideroblastic anemia → Vit B₆ deficiency.

4. Lead poisoning → as sideroblastic anemia.

5. Anemia of chronic illness. "Late stage".

The next step if you detect microcytic hypochromic anemia
* is iron study :- if TIBC "Total iron binding capacity" is high ⇒ it's IDA. "confirmative". you can also look for serum iron and serum Ferritin.

If all iron study are normal ⇒ it's thalassemia but have to confirm by electrophoresis.

* So Hemolytic anemia can cause microcytic hypochromic anemia by Thalassemia → The only cause of microcytic hypochromic anemia* before R_x + Reticulocytosis + normal iron study.

* Sideroblastic anemia & Vit B₆ deficiency → have abnormal iron utilization (↓ Heme formation) → ↑ iron in the Body → High iron study. confirmed by sideroblastic ring in cytoplasm of periphe Blood cells or B.M.

* Anemia of chronic illness → Normocytic normochromic. characterized by high erythropoietin and normal or low iron study.

TIBC → normal or low. and it's not Dimorphic anemia.

Microcytic hyperchromic anemia → Hereditary Spherocytosis

↑ MCHC

D/D of normocytic normochromic anemia :-

① ↓ Production → B.M. change or failure by infection or malignancy or fibrosis or aplasia.

↓ Erythropoiesis → by CKD or chronic inflammation by TNF α .

↓ Erythropoietin.

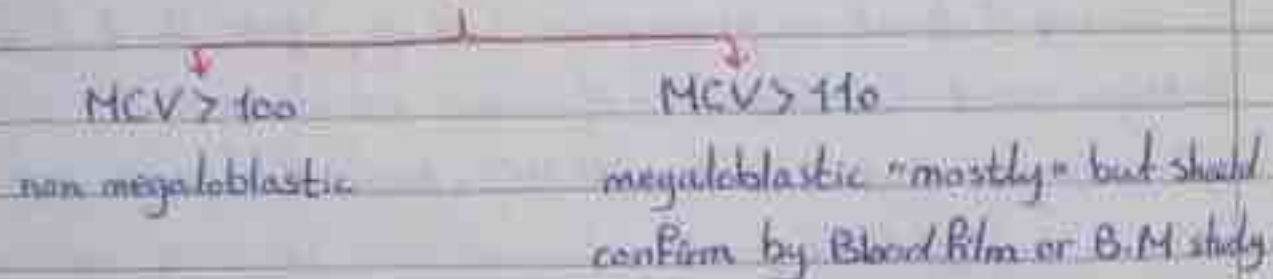
↓ Steroid & Androgens → by Adrenal insufficiency.

↓ ACEH → by hypopituitarism.

② ↑ Destruction → Hemolysis and Hemorrhage.

• But hemorrhage and hemolysis later on will lead to iron deficiency anemia because of utilization of iron stores from B.M. & liver.

Macrocytic cell



D/D of macrocytic megaloblastic anemia :-

1. ↓ Vit B $_9$ & B $_{12}$.

2. Drugs as metformin → interfere with absorption of vit B $_{12}$.

D/D of macrocytic non megaloblastic anemia :-

1. Alcohol. 2. chronic liver disease. 3. Hypothyroidism.

4. Pregnancy. 5. Myelodysplasia. 6. Other drugs.

7. DM 8. Hemolytic anemia. 9. Epilepsy.

Macrocytosis occur due to irregularity of cell membrane formation as a result of Dyslipidemia and defect in protein integration.

The mechanism of macrocytosis in hemolytic anemia is B.M compensation by $\uparrow$ Reticulocyte count in peripheral Blood $\Rightarrow$ Macrocytic non megaloblastic or due to depletion of Vit B₉ & B₁₂ (over utilization) $\Rightarrow$ But it's not megaloblastic.

Hemolysis $\Rightarrow$ There's RBC's destruction without anemia due to B.M compensation.

Hemolytic anemia $\Rightarrow$ There's RBC's destruction + Anemia due to Failure of B.M to compensate.

The next step if you detect Normocytic normochromic anemia is look for erythropoietin level and Reticulocyte count.

the do RFT, TFT, hemolytic study... etc. For underlying cause

Case 1 $\Rightarrow$ Patient on phenytoin therapy, presented with Fatigue and dizziness.

Hb = 6g, MCV = 123 FL, MCHC = 20%, Plt = 50,000,
WBC = 2000, RTx = 0.5.

It's pancytopenia due to Megaloblastic anemia, not aplastic because RTx count isn't zero, and MCV is high - but should confirm by doing B.M aspiration.

Case 2 $\Rightarrow$ Patient with long history of Rheumatoid arthritis, presented with Fatigue & Dizziness.

Hb = 6g, MCV = 80 FL, MCHC = 35%, Plt = 20,000,
WBC = 1000, RTx = 7%.

It's anemia 2^{ry} to hypersplenism, not anemia of chronic illness; because RTx isn't low.

Case 3 $\Rightarrow$ Patient on radiotherapy and azathioprine therapy, presented with Fatigue & Dizziness.

Hb = 6g, MCV = 80 FL, MCHC = 35%, Plt = 20,000, WBC = 1000, RTx = 0.

It's aplastic anemia, next step is Blood Film then B.M aspiration.

Case 4 $\Rightarrow$ Patient presented with Fatigue, Dyspnea, chronic Diarrhea and has RT iliac fossa mass, Pt also has neurological finding. Colonoscopy & Biopsy reveal non caseating granuloma.

CBC shows:- Hb = 6g, MCV = 123 FL, MCHC = 20%,

Plt = 50,000, WBC = 2000, RTx = 0.5% what's the cause of this finding? It's secondary to one of the following:-

- ☐ Folate deficiency.
- ☐ Use of medication as azathioprine in pt with crhen's disease.
- ☐ Steroid therapy.
- ☒ Malabsorption of vit B12.

Iron deficiency anemia

Def: Anemia due to decreased body iron.

Epidemiology: The most common anemia worldwide.

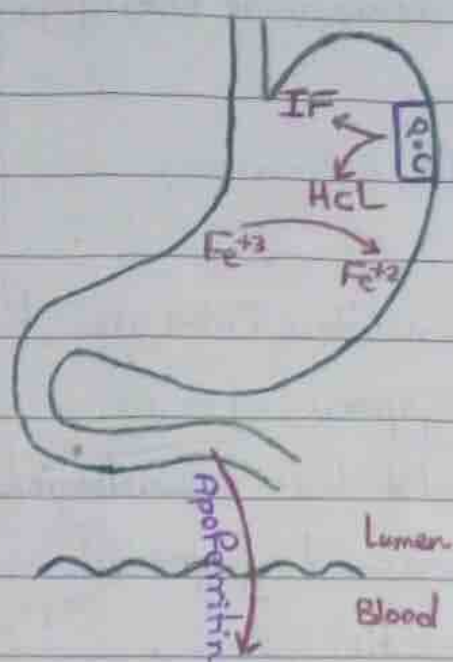
In men the most common cause of IDA is GIT Bleeding.

In women $\rightarrow$ Premenopausal is excessive menstrual blood loss.

Postmenopausal $\rightarrow$ GIT Bleeding.

Iron metabolism: Present in meat "Ferrous form" and green vegetables "Ferric form" $\rightarrow$ not well absorbed form.

Daily requirement $\Rightarrow$ 1-2mg, Pregnancy = 5mg.



Absorption :- First $\rightarrow Fe^{+3}$ "Ferric Form" will be absorbed to Fe^{+2} "Ferrous Form" by HCL. "Absorption is $\uparrow$ by acids as vitamin C & $\downarrow$ By tea." (inside the stomach).

• Then Fe^{+2} will be absorbed from duodenum and upper jejunum (By ApoFerritin from lumen to the blood).

• Then will be transported by Transferrin (carrier prt. synthesized from the liver) $\rightarrow$ transport iron & normally full 30% and 70% $\rightarrow$ empty. (Transferrin saturation).

• Once 30% is pulled $\rightarrow$ no more synthesis of Transferrin by the liver.

• And iron will be stored as Ferritin mainly in liver & B.M and muscle or stored as hemosiderin.

• Liver release Hepcidin to prevent further absorption & Transferrin saturation not exceed 30% of saturation.

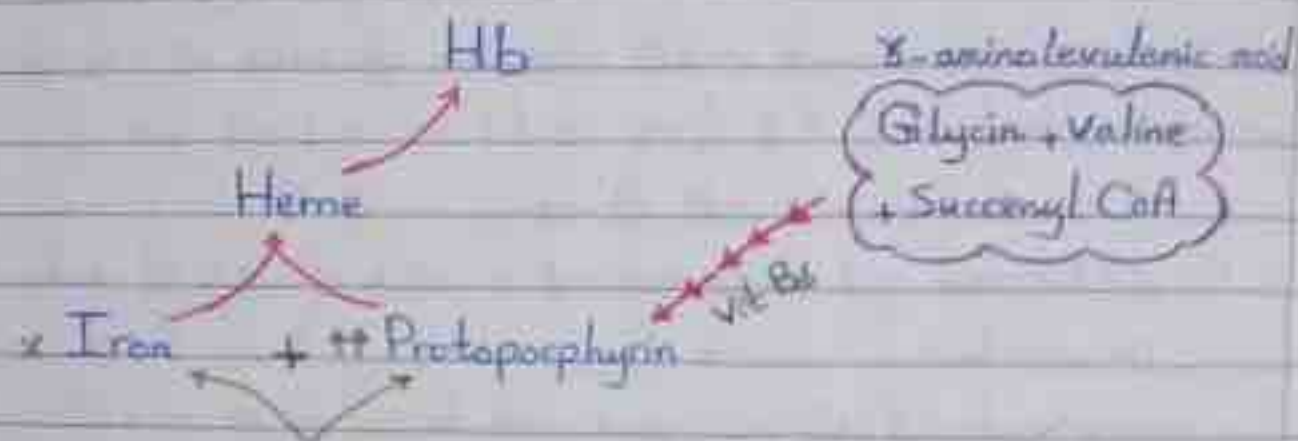
* If patient have any problem $\downarrow$ iron absorption as Parietal cell defect and GIT Blood loss $\rightarrow$ Transferrin will pull less than 30% $\rightarrow$ liver $\uparrow$ synthesis of Transferrin $\rightarrow$ $\uparrow$ incidence of empty transferrin ($\uparrow$ Capability to carry iron) $\rightarrow$ $\uparrow$ TIBC.

* Also upregulation of iron & Transferrin will occur $\Rightarrow$ Nowadays The best investigation test for Dx IDA but not widely available.

Note $\rightarrow$ Transferrin saturation = Binded (normally 30%).

Transferrin level = Empty = TIBC.

Etiology :- (1) Chronic blood loss (Most common cause)
 (2) ↓ Intake (2nd most common cause), ^{GIT blood loss}
 (3) ↓ Absorption $\Rightarrow$ Post gastrectomy, Proton pump inhibitors or pernicious anemia "Antiparietal cell Ab"
 (4) ↑ Demand $\Rightarrow$ Pregnancy, puberty



Vit B6 is important for conjugation B/w Iron & Protoporphyrin

- ↑ Erythrocyte protoporphyrin in peripheral blood due to ↓ of Iron
- ↓ Iron lead maturational arrest of erythropoiesis in step of transformation of Normoblast $\rightarrow$ Reticulocyte
- So, By B.M. aspiration $\rightarrow$ B.M. occupying by normoblast (not red for DE)
- Hereditary ↓ of Vit B6 or ↓ Absorption of Vit B6 or patient take Iron oxidase drug $\Rightarrow$ ↓ Formation of Protoporphyrin and Iron $\uparrow$ $\rightarrow$ Formed sideroblastic ring in B.M. Destroyed in peripheral blood.

Iron is important for oxidase catalyze enzyme $\rightarrow$ For Resolution and Regeneration. So absence of iron will results to:-

C/P of IDA $\Rightarrow$ General manifestations of anemia + the following:-

1. Hair loss.

2. Epithelial manifestations $\rightarrow$ Esophageal ulcer, Atrophic, smooth red tongue (painless Atrophic glossitis, Angular stomatitis, desquamated epithelial cell $\rightarrow$ esophageal web $\rightarrow$ Dysphagia.

3. Unexplained splenomegally (20%) in severe cases.

Plummer-Vinson syndrome (Patterson-Brown-Kelly syndrome) = Dysphagia (esophageal web) + Atrophic glossitis + Splenomegally. It carries high risk of post-cricoid cancer esophagus.

Cancer $\rightarrow$ Anemia

4. Pica: the craving to eat unusual substances such as dirt, clay, ice, or hair.

* Investigations $\Rightarrow$ (1) CBC (microcytic hypochromic anemia) $\downarrow$ Hb, $\downarrow$ Hct, $\downarrow$ RBC count, Reticulocyte is normal or $\downarrow$ (in severe cases) it's $\uparrow \rightarrow$ in 3rd day after P_x (Peak at 7 day of P_x). Platelet count is normal unless patient have got blood loss or menses $\rightarrow$ plt $\uparrow$ to compensate.

(2) Iron studies $\rightarrow$ Serum iron (least accurate).

Serum Ferritin $\rightarrow$ more accurate than serum iron.

B.M Hemosiderin or Ferritin $\rightarrow$ more accurate than Serum Ferritin.

Total iron Binding capacity (Transferrin level). (most accurate)

* Iron receptor level $\rightarrow$ The best and the most accurate test

(3) Blood Film $\rightarrow$ Target cells (Maximize hat) & Pencil cells due to small centralized Hb.

(4) B.M examination $\rightarrow$ $\uparrow$ Normoblast cells & $\downarrow$ Hemosiderin.

(5) Biochemistry (lab) $\rightarrow$ $\uparrow$ Protoporphyrin in RBC's.

Investigation For the etiology $\Rightarrow$ as coagulation profile, Upper & lower endoscopy, stool occult blood, Pelvic U/S
 * Unexplained anemia $\Rightarrow$ Call hematological consultant $\rightarrow$ if no cause is detected $\Rightarrow$ start Blind therapy $\rightarrow$ if there's no response $\Rightarrow$ Do invasive procedures.

Management:-

I) Correct underlying cause (The most important step) + Nutritional support.

II) Oral Iron $\Rightarrow$ Ferrous sulphate or Ferrous gluconate.

Advise patient to take it after meal (not on empty stomach) because it's acidic preparation, & patient should not have gastritis or peptic ulcer $\Rightarrow$ Contraindicated.

* Side effects $\Rightarrow$ Nausea, Abdominal pain, Black stool, teeth discoloration, Diarrhea or constipation, Metallic taste.

* Note $\Rightarrow$ Hb $\uparrow$ 1g every 1 week $\rightarrow$ by whatever the route (oral or parenteral)

It is continued for 3-6 months after the Hb has returned to replenish iron store.

III) Parenteral preparation (IM or IV) as "Sorbitol & Dextan" used only with patients who are unable to tolerate oral therapy (has gastritis or peptic ulcer) or patient with malabsorption. Parenteral route doesn't lead to more rapid repair of anemia.

Side effects $\Rightarrow$ Anaphylaxis, phlebitis, skin discoloration, pain.

IV) Blood transfusion $\Rightarrow$ It's appropriate only with severely symptomatic patient as Heart failure pt. or patient with comorbidities as

COPD and CKD, or to prepare patient for surgery.

Blood transfusion ↑ Hb rapidly.

* **Monitoring:-** Reticulocytosis starts on 3rd day & Peaks at 7th after starting Rx. (↑ RDW → Anisocytosis).

Hb ↑ by rate of 1g/dl/wk.

D/D of refractory IDA "orally" :-

- ① Poor compliance. ② Low dose. ③ Malabsorption.
- ④ Wrong Dx. ⑤ Persistent underlying cause.
- ⑥ Dimorphic anemia. ⑦ Anemia of chronic illness.

* Patient with anemia of chronic illness, if presented with microcytic hypochromic anemia will not improve by oral iron because of high level of hepcidin.

and treated as treatment of anemia of chronic illness

+ TNFα Blocker + erythropoietin to stimulate R.M synthesis

but should give iron before erythropoietin to avoid severe

depletion of iron from the body. (Iron before erythropoietin by 1 mo)

* ex:- long standing Rheumatoid arthritis → Hepcidin is ↑↑ will not improve by iron Tab.

Note → Iron sulphate contain only 65mg of iron.

IDA patient absorb 195mg iron / 24 hr except anemia of chronic illness because of high hepcidin.

Anemia of chronic illness...

Def: It's anemia that occurs in patients with chronic inflammation (Malignancy, Autoimmune as RA, Infection as T.B).

All these $\uparrow$ TNF $\rightarrow$ its effects are mentioned before.

It's the most common anemia in elderly.

Dx: CBC $\rightarrow$ Normocytic normochromic "usually", in late stage maybe $\rightarrow$ hypochromic microcytic.

① Iron studies $\rightarrow$ $\downarrow$ Serum iron level $\rightarrow$ due to $\uparrow$ hepcidin.

• Normal or high serum Ferritin level $\rightarrow$ Because not used by B.M due to $\downarrow$ of erythropoietin or become insensitive.

• TIBC $\rightarrow$ Normal or $\downarrow$.

• Erythropoietin level is $\downarrow$.

Rx: ① Detect why pt have anemia of chronic illness & Rx the underlying cause.

② TNF Blocker For autoimmune pts.

Infliximab C/I For T.B pt.

③ Exogenous erythropoietin $\rightarrow$ but give iron parentally before.

Sideroblastic anemia...

Def: Abnormal utilization of iron with protoporphyrin characterized by trapped iron in RBC's names ringed sideroblastic causes: - Hereditary $\downarrow$ of vit B₆ or 2ry to Isoniazide or lead poisoning.

Dx: $\rightarrow$ CBC $\rightarrow$ microcytic hypochromic.

• Iron studies $\rightarrow$ $\uparrow$ serum iron level, $\uparrow$ Transferrin saturation $\uparrow$ Ferritin level.

* B.M reveals $\rightarrow$ Ringed sideroblastic.

Rx :- Pyridoxine $\rightarrow$ hereditary causes.

Stop the offending drug.

Megaloblastic Anemia

Def :- A group of anemia caused by deficiency of B_{12} or Folic acid.

$\downarrow$ Production of mature RBC $\rightarrow$ Megaloblastic cells inside the B.M, some of them will escape to the peripheral blood.

This megaloblastic cells will be destroyed by Spleen $\rightarrow$ and release $\uparrow K + LDH$ Level. also can be destroyed inside the B.M.

So $\uparrow K + LDH$ not always mean hemolysis.

* Characteristic Features :-

① Megaloblastic in B.M $\rightarrow$ intramedullary hemolysis.

② Macrocytic RBC in peripheral blood. (Oval in shape).

③ Ended by pancytopenia with hyper-segmented neutrophil.

1st sign appear in peripheral blood film is hypersegmented neutrophil, because neutrophil has short life span $\rightarrow$ 6 hrs.

& divided rapidly & need vit B_{12} very rapid.

but it's not the 1st one to cause symptoms.

④ Improved by vitamin (B_9 & B_{12}) replacement.

⑤ Associated with (Neurological and GIT manifestation).

* Important notes :-

Homocysteine $\xrightarrow{\text{Vit } B_9 \text{ \& } B_{12}}$ Methionine

Methyl-Malonic acid $\xrightarrow{\text{Vit } B_{12}}$ Succinyl CoA

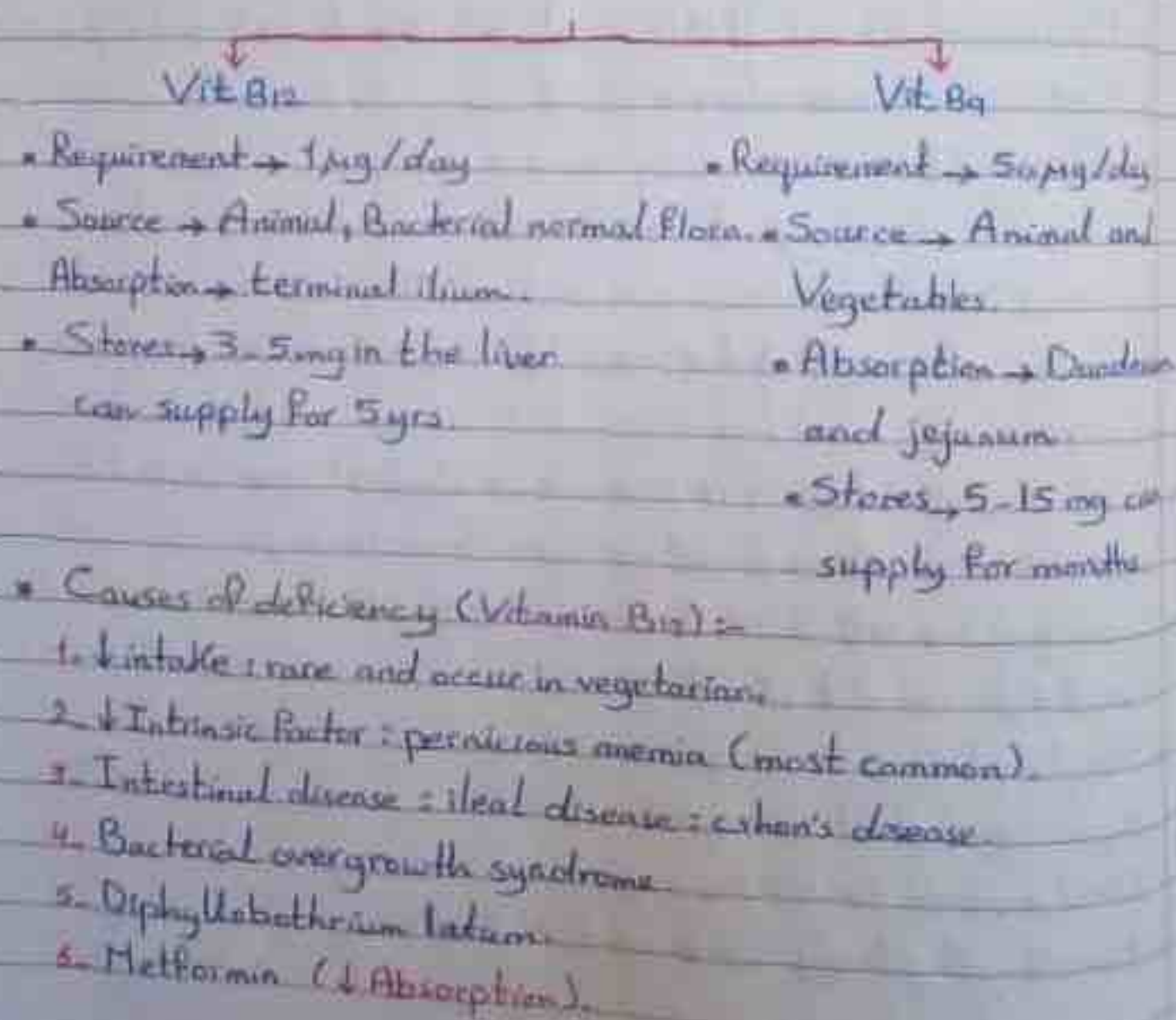
Dihydrofolate (DHF) $\xrightarrow{\text{Vit } B_{12}}$ Tetrahydrofolate (THF)

If patient have homocystenemia, how to differentiate the cause is Vit B₁₂ or Vit B₉ deficiency?

Look for Methyl-Maleic acid - specific - & The best single blood test for Vit B₁₂ deficiency.

If patient with vit B₁₂ deficiency & misdiagnosed as vit B₉ deficiency and treated by Folate (DHF) → Vit B₁₂ will be severely depleted → 1. Nerve demyelination → severe neurological manifestations → **Called Folate trap.**

Metabolism



* Causes of Vit B₁₂ deficiency:-

1. ↓ intake, alcoholic, elderly.
2. Celiac disease.
3. ↑ Demand → pregnancy.
4. Drugs:- Phenytoin, Methotrexate, Azathioprine, Metformin, Bactrim, Pyrimethamine.

C/P → General symptoms & signs of anaemia, GIT manifestation + Neurological manifestations:- Vit B₁₂.

1. Peripheral neuropathy.
 2. Pyramidal lesion (UMNL).
 3. Post column sensation loss.
 4. Ataxia (Motor).
- } → Subacute combined degeneration

Note → The neurological manifestations are not correlated to severity of anaemia.

* Neurological manifestations could be appear before symptoms of anaemia.

* Rx of anaemia doesn't improve neurological symptoms if the megaloblastic anaemia is lasting more than 90 days.

* Investigations:- ① CBC (macrocytic, hyperchromic).

Reticulocyte count ↓, ESR ↑.

② Peripheral Blood changes:-

- * Hyper-segmented neutrophil.
- * Oval macrocytosis RBC.
- * Howell-Jolly body (survivor of DNA).

Bone marrow: hyperplastic with megaloblastic RBCs.

Lab: ↑ homocystein in both vit B₉ & vit B₁₂ deficiency.

↑ Methylmalonic acid only in vit B₁₂ deficiency. (Diagnostic)

Challenge test: Vit B₁₂ and IF form a complex in stomach. This complex is protective for vit B₁₂ against HCL. Then complex will transfer to small intestine and once reach the alkaline media → splitting & vit B₁₂ will be absorbed and transfer to the blood by cyanocobalamin.

• How to know by this test if the malabsorption is 2nd to gastric cause or intestinal cause?

- By coverage of all cyanocobalamin carriers → by high dose of vit B₁₂ IM → then give radiolabel vit B₁₂ orally → if absorbed → release in the urine.

If not absorbed → Defect in stomach or terminal ileum.

Give vit B₁₂ radiolabel + IF → Absorbed → stomach problem not absorbed → Terminal ileum problem.

• Patient with pernicious anemia take vit B₁₂ orally + IF or Parentally IM injection. but if pt have bleeding tendency or whatever the C/I for injection → Give him high dose vit B₁₂ "orally" without IF → it will be absorbed because HCL can't destruct all high dose of vit B₁₂.

• Treatment → 5 days Vit B₁₂ + Folic acid.

Hemolytic Anemia ---

Immature destruction of RBC.

Hemolysis :- RBC life < 120 days, (shortening of RBC's life span).

B.M can increase production of RBC by 8 times, but when it fails to compensate anemia develops.

* Types of hemolysis :-

1. Extravascular Hemolysis - (Spleen, B.M, liver).

2. Intravascular Hemolysis.

* Splenectomy have a role in extravascular type only.

* Antibodies of autoimmune disease can affect The RBC's at body temperature $37^{\circ}\text{C} - 38^{\circ}\text{C}$ $\rightarrow$ Warm autoimmune hemolytic anemia or at 4°C $\rightarrow$ Cold autoimmune hemolytic anemia.
Cold AIHA occur in periphery of the Body $\rightarrow$ Intravascular
Warm AIHA occur inside the spleen $\rightarrow$ Extravascular.

* **Hemolysis in general** $\rightarrow$ RBC destruction will release in serum (K, LDH, bilirubin).

* Features :- 1. Anemia + high reticulocyte.

2. Jaundice (indirect bilirubin).

3. Splenomegally (usually in extravascular)

Splenic destruction not present in all types of hemolytic anemia, but all cases have splenomegally because it's occurs either due to RBC destruction «extravascular» or due to extramedullary hematopoiesis «intravascular».

Hemolytic anemia may be associated with $\downarrow$ Reticulocyte in case of Aplastic crisis due to depletion of vitamins or infection by parvovirus B19.

• Extravascular hemolysis :-

- The RBC are removed by macrophages of the reticuloendothelial system mainly in spleen (splenomegally).
- Breakdown of Hb $\uparrow$ unconjugated bilirubin Jaundice.
- The high bilirubin will be excreted by liver $\uparrow$ risk of pigment gall stones (liver can conjugate excess bilirubin 6 times than normal). One of the causes of abdominal pain in case of hemolytic anemia.
- Urine $\uparrow$ urobilinogen (not bilirubin). & $\uparrow$ stercobilinogen in stool (Dark).

Intravascular hemolysis :-

- Fragmentation of RBC within the circulation (schistocyte). Free Hb bind to Haptoglobin. Form a complex removed by the liver, so in hemolytic anemia Free Haptoglobin level is $\downarrow$. When the capacity of haptoglobin is exceeded, Free Hb is oxidized to form methemoglobin which binds to albumin forming methemalbumin, detected by the Schumm's test by Spectroscopy. If all the above protective mechanisms are overloaded, Free Hb filtered by the kidney and converted to hemosiderin in renal tubular cell (hemosiderinuria) detected by Prussian blue stain of sloughed tubular cell in urine. After that Hemoglobinuria (hemoglobin in urine) Black urine.

Causes of hemolytic anemia:-

* Congenital:-

1. Membrane defects $\rightarrow$ Spherocytosis, Elliptocytosis.
2. Hemoglobinopathies $\rightarrow$ Sickle cell disease, Thalassemia.
3. Red cell enzyme defects $\rightarrow$ G6PD deficiency, Pyruvate Kinase deficiency.

* Acquired:-

1. Autoimmune (warm, cold).
 2. Infections: EBV, Mycoplasma. $\rightarrow$ cold type
 3. Systemic lupus erythematosus (SLE).
 4. Chronic lymphocytic leukemia (CLL). $\rightarrow$ Warm type
- Note: pneumonia + Hemolysis = Mycoplasma $\rightarrow$ not respond to penicillin & cephalosporins.
- * Most common cause of death in CLL patient is infection.
 - * CLL can cause autoimmune hemolytic anemia + autoimmune thrombocytopenia = Evans syndrome.
 - * patient of CLL if doesn't have anemia or thrombocytopenia $\rightarrow$ only conservative Rx.
 - * Cortisone have a role in Autoimmune hemolytic anemia, if cortisone is failed $\rightarrow$ Do Splenectomy for warm type & warming hands of cold type.
2. Non-immune
 1. Microangiopathic hemolytic anemia (MAHA)
 2. Prosthetic heart valve
 3. Paroxysmal nocturnal hemoglobinuria (PNH).

- Cell membrane RBC receptors (CD47, CD55, CD59) → protect RBC's from Free radicals and hypoxemia During night (due to ↓ R.R.). These receptors are absent in PNH patient, so RBC's will not tolerate even mild hypoxemia especially inside the veins because O_2 inside the vein is less than artery. During night → ↑ RBC's destruction → ↑ Hb → Filtered Free Hb from the Kidney → Dark urine. (by 1st micturition at the morning only). Then WBC's & Plt. will be destructed also → Pancytopenia. So patient become risky for infection & Bleeding. also ↑ RBC hemolysis is risky for vein occlusion → ischemia. DVT & recurrent abortion may occur & Brain stroke may occurs 2nd to Cavernous sinus thrombosis.

Rx of PNH → Monoclonal Antibody (Eculizumab).

4. Drug or toxin-induced (Direct cause).

Note: Extra vascular hemolysis → Autoimmune warm type, Membrane defects, Hemoglobinopathies.

Intravascular hemolysis → Red cell enzyme defects

↳ No splenomegally unless extramedullary hematopoiesis is associated

- **Clinical Features:-** Anemia, Jaundice (unconjugated bilirubin), Splenomegally, Gall Bladder stones, ischemia in crisis, bone changes or pain.

- Investigations → Hb → Anemia

MCV, MCH → Normocytic or macrocytic

Reticulocytes → Reticulocytosis.

Bilirubin $\rightarrow$ unconjugated.

LDH $\rightarrow$ Release from destructed RBC.

Haptoglobin (Free) $\rightarrow$ Reduced or absent.

Blood Film $\rightarrow$ Polychromasia (Reticulocytosis) & Poikilocytosis.

B.M $\rightarrow$ Erythroid hyperplasia of the B.M.

Urine $\rightarrow$ Urobilinogen (extravascular)

$\rightarrow$ Hemosiderin (Intravascular)

$\rightarrow$ Hemoglobin (Intravascular)

* Very important notes :- The anemia gradual and chronic (crisis start).

1- Hemolytic crisis $\rightarrow$ worsening of anemia symptoms.

2- Megaloblastic crisis $\rightarrow$ neurological symptoms develop.

3- Aplastic crisis $\rightarrow$ severe anemia, recurrent infection & Bleeding.

4- Sequestration crisis $\rightarrow$ vein congestion & occlusion (pain).

5- Vasoocclusive crisis $\rightarrow$ ischemic pain (Abdominal, chest... etc.)

* Causes of hemolytic crisis :-

[1] Infection

[2] Fever

[3] Dehydration

[4] PH disturbance

[5] Stress

[6] Hypoxia

[7] Drugs

[8] Food.

* Diagnosis of Hemolytic crisis :-

Clinically $\rightarrow$ worsening of all symptoms of anemia + Fever.

Lab $\Rightarrow$ • Rapid drop in Hb

• Severe elevation in Reticulocytes.

• Elevation of (HDL, K, Bilirubin).

Treatment $\rightarrow$ TUC.

- Infection $\rightarrow$ Antibiotics.
- Dehydration $\rightarrow$ Rehydration.
- Fever $\rightarrow$ Paracetamol.
- PH disturbance $\rightarrow$ Correction (HCO_3^-).
- Hypoxia $\rightarrow$ Oxygen.
- Drugs & Food $\rightarrow$ Avoidance.
- Supportive Blood transfusion $\rightarrow$ if having severe drop in Hb.

Note $\rightarrow$ Fever in hemolytic crisis not always consider as a cause, maybe occurs 2^{ry} to hemolytic crisis like after dehydration & results to $\uparrow$ PGs & cytokines $\rightarrow$ Fever.

- * Megaloblastic crisis :- Occurs due to consumptions of vitamins (B_9 & B_{12}) during hemolytic crisis.

characterized by :-

- Low reticulocyte.
- MCV very high > 120 fl.
- Megaloblastic changes in B.M.
- Elevation of homocysteine.
- Lastly pancytopenia.

To differentiate between pancytopenia of megaloblastic and aplastic anemia $\rightarrow$ look at MCV, if it's > 120 fl.

most probably is megaloblastic $\rightarrow$ confirm by B.M examination.

- Should give vitamins as supportive in pt with hemolysis.

- * Aplastic crisis :- This is usually occurs 2^{ry} to viral infection (para-virus B19).

characterized by :-

- Deterioration of anaemia symptoms.
- $\downarrow$ Reticulocytes (maybe = 0).
- Pancytopenia.
- Normocytic normochromic.
- Aplastic B.M.

Aplastic crisis is poor prognosis $\rightarrow$ Alred B.M transplantation

Management of hemolytic anemia :-

Generally include :- 1. Blood transfusion especially for Haemoglobin (regular)

2. Iron chelating agent: Desferrioxamine (SC) to prevent or delay hemosiderosis.

3. Splenectomy (extravascular type) Followed by SHEN vaccine (strept pneumonia, H. influenza, Neisseria (2-3 wks before splenectomy). Antibiotic maybe given after splenectomy for life.

4. Folic acid and vit B12 replacement to restore demand.

5. Corticosteroid, $\pm$ immunosuppression for auto-immune hemolysis.

6. Treatment of the cause & avoid the triggered factors.

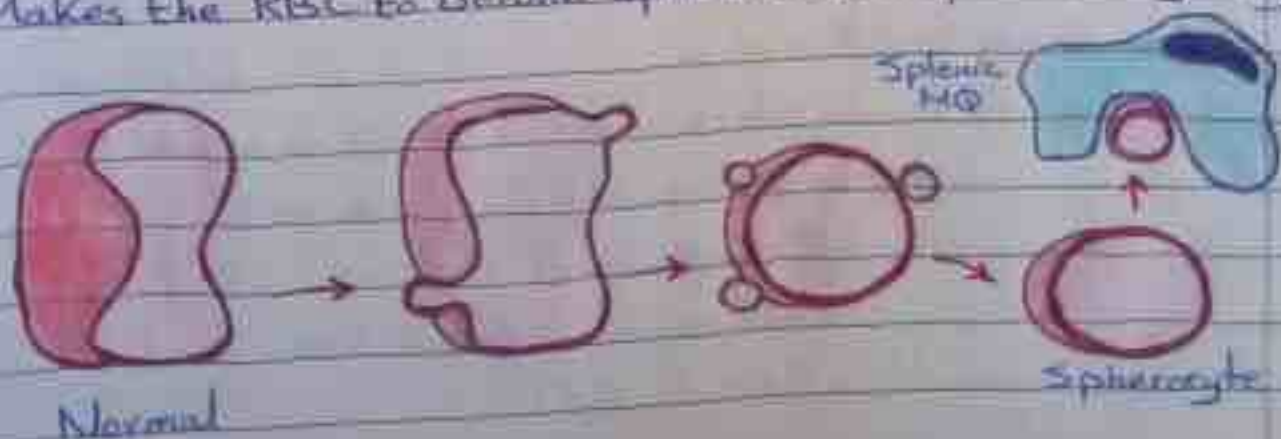
Hereditary spherocytosis...

The most common inherited hemolytic anemia.

Inheritance is Autosomal dominant.

There is abnormality RBC membrane protein spectrin or Ankyrin.

Makes the RBC to become spherical in shape with rigidity



• Hereditary spherocytosis → Paragraph from powerpoint

Etiology ⇒ mutations in spectrin, ankyrin, and band 3.

General Features ⇒ Autosomal dominant, 20% mutation.

Spherocytes in peripheral blood.

High reticulocyte count.

Splenomegally (500-1000 gm).

Mildly elevated indirect bilirubin.

↑ Osmotic fragility especially after incubation for 24 hrs at 37°C (in hypotonic).

Splenectomy helps in correcting anemia. (not curable).

• Clinical presentations :- Most cases asymptomatic

1. Anemia (Weakness, Dyspnea, Palpitations, Pallor) + Jaundice + Splenomegally.

2. Pigmentary gall stones are present in 50% of patient & may cause cholecystitis.

Note ⇒ Don't do cholecystecomy before splenectomy in case of hemolysis, because pigmentary stones will descend into CBD → obstructive jaundice → & may cause Ascending cholangitis → which is fatal.

3. Ankle ulcers.

4. Aplastic crisis associated with parovirus B19 infection may occur.

• Investigations :- As all hemolytic anemia (anemia, Reticulocytosis, indirect hyperbilirubinemia).

1. CBC : Microcytosis with hypochromia.

2. Blood film (spherocytosis).

3. Osmotic fragility test is +ve $\rightarrow$ Diagnostic.

When RBC are added to hypotonic solution the RBC are abnormally fragile.

4. Flow cytometry $\rightarrow$ For spectrin & Ankyrin proteins.

* Treatment $\Rightarrow$ 1. Splenectomy improves the decrease in lifespan but spherocytosis persists, because it's origin from B-M.

2. Folic acid prophylaxis for life, because folate will be depleted.

3. cholecystectomy if required. (After splenectomy).

Note $\Rightarrow$ Perform splenectomy also to decrease risk of recurrent gallstones.

* Management of pt. For splenectomy $\Rightarrow$

Splenectomy should be delayed until the child is > 6 yrs.

The risk of invasive infection caused by encapsulated bacteria.

Vaccination $\Rightarrow$ Pneumococcal, Hemophiles influenza,

Meningococcal & influenza vaccines.

2-3 weeks before splenectomy.

Pneumococcal repeated every 5 yrs & influenza annually.

life-long prophylactic penicillin [if penicillin-allergic

give erythromycin].

Encapsulated bacteria $\Rightarrow$ Hemophiles influenza type B,

Strept. pneumoniae, Meningitidis, Group B streptococci,

Klebsiella pneumoniae, salmonella typhi.

Note $\Rightarrow$ Asplenic (No spleen) patient also risky for viral

infection as (influenza virus & HBV).

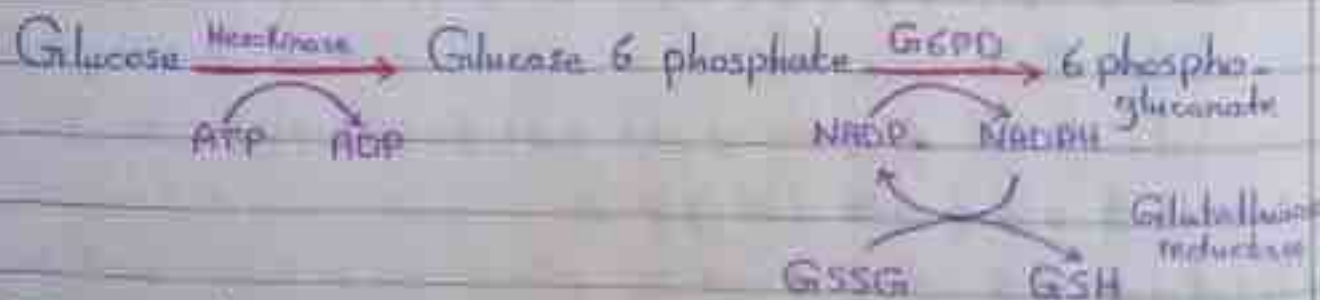
Glucose-6-phosphate dehydrogenase deficiency (G6PD) ...

- It's the most common RBC enzymatic defect.
- It may occur as acute hemolytic disease induced by infection or medications $\rightarrow$ otherwise stable. 😊
Chronic hemolytic disease can develop, if pt is uncontrolled.

Epidemiology $\rightarrow$ X-linked recessive Female just carrier male affected.

Mediterranean, Arabic, Asian & Africa.

Pathophysiology $\rightarrow$ G6PD enzyme synthesizes NADPH which protects the RBC from oxidative stress via reduced glutathione. So G6PD deficiency increases RBC damage on exposure to oxidants.



• Triggers of hemolysis :-

1. Infection.

2. Fava beans.

3. Drugs :- Antibiotic : sulphonamide, Nitrofurantoin, ciprofloxacin, dapsone.

Sulicylates.

Antimalarial. Quinidines.

* Clinical Features :-

Symptoms occur 24-48 hrs after exposure to oxidant.

Hemolysis occurs, resulting in :-

1. Abdominal pain, Fatigue.
2. Vomiting and Diarrhea.
3. Fever and jaundice.
4. Hepatosplenomegaly maybe present. (after long standing and recurrent attacks).

* Laboratory Finding :- 1. Hemoglobinuria.

2. Blood Film : Bite cell (RBCs with part of membrane missing).
& Heinz bodies.



Bite cell



Heinz body

* Dx by :- Low level of G6PD in RBCs. (During remission).
because G6PD enzyme deficiency occurs after release of RBCs
by at least 40 days, due to compensation of hemolysis by B.M
(early) $\rightarrow$ $\uparrow$ reticulocytes (which have normal enzyme level).
So don't measure it during crisis.

* Treatment :-

1. Stop triggered Factors.

Transfusion as needed.

Splenectomy not beneficial. (Because it's intravascular
Hemolysis type).

Types of hemoglobin...

1. HBA $\rightarrow$ 2 alpha + 2 beta = >97% of adult HB.
2. HBA₂ $\rightarrow$ 2 alpha + 2 delta = 1.5 - 3% of adult HB.
3. HBF $\rightarrow$ 2 alpha + 2 gamma = 0 - 1.5% of adult HB.

Note After birth by 6 months $\rightarrow$ HBF will be replaced by HBA
 So β -thalassemia & Sickle cell anemia doesn't occur before 6 months of age.

- Hydroxyurea is benefit as Rx of Sickle cell anemia because it's $\uparrow$ HBF which resists sickling
- HBA₂ $\uparrow$ in thalassemia major, not in Sickle cell anemia
 HBA₂ = N $\rightarrow$ Sickle cell anemia. HBA = 0 $\rightarrow$ Sickle cell major
 Normal

Sickle cell disease...

Epidemiology :- Autosomal recessive

- More in black, equal in sex.
- Age $\rightarrow$ it's start after 6 months of life, not before that because of HbF is strongly protective.

Pathophysiology :- S.S. disease is caused by a single amino acid substitution valine for glutamic acid on the number 6 position of the beta globin chain.

- The mutation results in polymerization of Hb when the RBC is exposed to low oxygen or acidosis.

(Hb F strongly resists polymerization).

- Types of Sickle cell mutation :-

1. S.S. disease (Hb SS)

two genes for Hb S (homozygous) 2 beta chain affected.

2. SS trait (Hb AS)

One gene for Hb S (heterozygous)

they have no anemia and the red cell morphology is normal, but resistant to *Plasmodium malariae*.

Note → when patient presented with anemia + jaundice, should ask about travel Hx; because malaria & antimalarial drugs can induce hemolysis.

- chloroquine drug should be taken before travel by 2 wks, during travel & after travel by 2 wks.

- Polymerization of Hb results to:-

1. Sickle shaped RBC → ↓ life span (Hemolysis).

2. Occlusion of small vessels → Ischemia & infarction.

- Venous occlusion is more common → as splenic vein → Splenic congestion & infarction (↑ intracapsular pressure) → recurrent splenic infarction → Autosplenectomy.

- Splenomegally in child age. & autosplenectomy in adult age.

Clinical presentation:-

1. Chronic hemolytic anemia.

2. Crisis.

Sickle cell crisis → **III Vaso-occlusive crisis** (most common crisis)

→ Extremely painful crisis.

→ Bone infarction in children hands & feet affected (Dactylitis).

→ Other bones are affected more in adult (Pain embolism).

as long bones & neck of femur.

2] Acute chest syndrome (sickle chest syndrome).

→ The most common cause of death in adult with sickle cell disease.

Bone marrow infarction (thrombotic crisis) → Fat emboli to the lung → sickling and infarction of the lung & fatal if untreated.

3] Sequestration crisis

→ Thrombosis of venous outflow lead to acute painful enlargement organ.

→ In children the spleen is the most common site (splen megalaly).

Adult → autosplenectomy occur.

→ In adult the liver is most common site, may lead to infarction.

4] Aplastic crisis

Caused by infection with * parvovirus, or Folic acid deficiency.

characterized by → Sudden fall in hemoglobin + low reticulocyte count.

* Sickling crisis precipitated by & treated by :-

1- Hypoxia → Oxygen

2- Dehydration → Intravenous fluids

3- Infection → Antibiotics

4- Stress → Opiate analgesics

* Features of sickle cell disease (very important) :-

1- Splenic infarcts (autosplenectomy) lead to pneumococcal infection.

2- Salmonella osteomyelitis occurs in areas infarcted bone

3- Pigmented gall stones are common. >50%

4. Priapism: painful sustained erection. $\rightarrow$ up to gangrene

D/D $\rightarrow$ SCD and CML.

5. Pregnancy is dangerous. $\rightarrow$ Placental occlusion.

6. Retinopathy.

7. Renal acute papillary necrosis $\rightarrow$ intravascular hemolysis.

8. Leg ulcers may occur.

* IF one of the previous points is present $\rightarrow$ the name will change from Sick cell anemia to Sick cell disease

Case 1 $\rightarrow$ 16 years old black male, presented with severe bone pain and dyspnea, chest pain, CBC shows anemia and hemoglobin electrophoresis shows: $\text{Hb A} = 0\%$, $\text{Hb F} = 55\%$, $\text{Hb A}_2 (1.5\%)$. What's the Dx?

A. Sick cell anemia.

B. Sick cell trait.

C. Sick cell disease. $\checkmark$

D. Beta thalassemia

Case 2 $\rightarrow$ Hemoglobin electrophoresis shows: $\text{Hb A} = 30\%$, $\text{Hb F} = 55\%$, $\text{Hb A}_2 (1\%)$. What's the Dx?

A. Sick cell anemia.

B. Beta thalassemia minor.

C. Sick cell trait. $\checkmark$

D. Beta thalassemia major.

Case 3 $\rightarrow$ Hemoglobin electrophoresis shows: $\text{Hb A} = 0\%$, $\text{Hb F} = 55\%$, $\text{Hb A}_2 (20\%)$. What's the Dx?

- A. Sickle cell anemia.
- B. Sickle cell trait.
- C. Sickle cell disease.
- D. Beta thalassemia major. ✓

Case 4 $\Rightarrow$ Hemoglobin electrophoresis shows :-

HB A = 30% , HB F = 55% , HB A₂ (15%).

What's the Dx?

- A. Sickle cell anemia.
- B. Beta thalassemia minor. ✓
- C. Sickle cell disease
- D. Beta thalassemia major.

Investigations :-

As all hemolytic anemia (Anemia, Reticulocytosis, indirect hyperbilirubinemia).

- CBC $\Rightarrow$ Normocytic normochromic anemia, leukocytosis (common).
- Blood Film $\Rightarrow$ Sickle cells + Features of (hyposplenism).
($\uparrow$ Howell jolly bodies due to autosplenectomy).
- HB electrophoresis shows 80-90% HbS with no or normal Hb A but Hb F maybe elevated $>1.5\%$. (This test confirm Dx).

Note $\Rightarrow$ The Hb A₂ is not $\uparrow$, unlike beta thalassemia in which Hb A₂ is $\uparrow$.

Treatment :- • Treatment of crisis & avoid precipitating factor of crisis.

Hydroxyurea (hydroxycarbamide) a chemotherapeutic agent that $\uparrow$ Hb F $\rightarrow$ given for recurrent crisis.

- Daily oral penicillin prophylaxis is started in the first months up to 5 years of life to ↓ the risk of *S. pneumoniae* infection. & Daily folic acid is given to prevent folic acid deficiency & aplastic anemia.
- Vaccination: against (SHIN) *S. pneumoniae*, Hemophilus, Influenza, *Neisseria meningitidis* & Hepatitis B.
- Blood transfusion may indicated → Aplastic crisis or multi-organ failure.
- Bone marrow transplant for young is therapeutic option.
- Prognosis:-
Median life expectancy is in the forties & cause of death (infection, stroke, RE, HF, Pulm. HTN).
Pulm. HTN is due to hypoxemia → pulmonary vasoconstriction.
- Long term complications include:-
 - Delayed growth & puberty and poor wound healing → vascular occlusion.
 - Cor pulmonale & cardiomegaly → hemosiderosis (due to iron overload exogenous by Rx and endogenous by recurrent hemolysis).
 - Gallstones.
 - Avascular necrosis of the femoral and humeral heads, and diminished cognition.
- Imp. note → Sickle cell disease is defect in quality not quantity → so it's mutation not deletion.

Thalassemia ...

Def:- Thalassemia is an autosomal recessive syndrome of anemia's characterized by defective synthesis of one of Hb chains. $\rightarrow$ defect in quantity (Deletion).

Pathophysiology:- Normally the major Hb in RBCs is Hb A ($2\alpha + 2\beta$), other hemoglobins present in small amounts are Hb A₂ ($2\alpha + 2\delta$) & Hb F ($2\alpha + 2\gamma$).

- ✓ Alpha-Thalassemia $\rightarrow$ results from defective alpha-globin chain synthesis (can occur intrauterine). defect in chromosome 16
- ✓ Beta-Thalassemia $\rightarrow$ results from defective beta globin chain synthesis.

Both types of thalassemia $\rightarrow$ hemolysis $\rightarrow$ $\uparrow$ bone marrow activity $\rightarrow$ bone marrow hyperplasia $\rightarrow$ $\uparrow$ in the size of bones in the face and skull (occurs with uncontrolled patients)

• Alpha-Thalassemia:- More in asian

There are 4 alpha-globin genes per cell (every 1 chain is coded by 2 genes). So there are 4 disease states:-

1. Silent carrier $\rightarrow$ 1 alpha-globin gene is deleted. Patients have no anemia.
2. Alpha-thalassemia minor $\rightarrow$ 2 alpha-globin genes are deleted. patients mildly anemic.
3. Hb H disease $\rightarrow$ 3 alpha-globin genes are deleted. Anemia is lifelong and severe $\rightarrow$ it's complicated by H.F due to severe anemia and 2nd to hemosiderosis.

This patient need regular monitoring & Blt transfusion

11. Fetal hydrops $\Rightarrow$ 4 alpha-globin genes are deleted - causes fetal death.

• Beta-Thalassemia :- More in Mediterranean

There are only two beta-globin genes per cell, so there are only two disease states :-

✓ Beta-Thalassemia major (Cooley's anemia or homozygous beta thalassemia) both genes for beta globin are abnormal. also called thalassemia intermedia.

✓ Beta-Thalassemia minor (heterozygous beta thalassemia or beta thalassemia trait) $\rightarrow$ Asymptomatic & accidentally discovered.

• Clinical Features :- Disease begins in infancy around 6 months of age.

1. Anemia + jaundice + Hepatosplenomegaly.

If untreated, bone marrow hyperplasia $\rightarrow$ Thalassemia facies = Mongoloid facies (Frontal bossing, prominent cheek bones due to maxillary hyperplasia).

Failure to thrive or growth retardation (Dwarfism).
& maybe subfertility & ulcer ulcers may occur.

• Investigations :- As all hemolytic anemia's (Anemia, Reticulocytosis (but here not severe enough to change the difference between size of RBCs $\rightarrow$ no anisocytosis). Indirect hyperbilirubinemia.

CBC : severe hypochromic and microcytosis, RDW $\rightarrow$ normal.

Electrophoresis : investigation of choice $\rightarrow$ low or absent Hb A and elevated Hb F & Hb A₂.

Blood Film :- show Target cells (Mexican cap).

Note $\rightarrow$ All microcytic hypochromic diseases may show target cells in blood film.

• β -thalassaemia minor characterized by hemolysis without anemia, while β -thalassaemia major characterized by hemolytic anemia (hemolysis + anemia)

Skull x-ray shows $\rightarrow$ "hair on end" appearance

D/D $\rightarrow$ 1) Thalassemia

2) Multiple myeloma

* Treatment $\rightarrow$ Regular blood transfusion, maintain Hb around 9g - 10g/dL (not more, to avoid iron overload).

& splenectomy often needed (to $\downarrow$ rate of hemolysis).

Complication $\rightarrow$ 1) Iron overload (hemosiderosis $>$ 10yrs old) to liver, heart, pancreas, pituitary, parathyroid.

Note $\rightarrow$ Pituitary iron overload $\rightarrow$ 2^{ry} hypogonadism $\rightarrow$ Infertility.

2) Volume overload

3) Infectious diseases

4) 2^{ry} Amyloidosis

5) 2^{ry} Inflammation & reaction.

Desferrioxamine $\rightarrow$ can chelating iron and $\uparrow$ its excretion in urine & delay hemosiderosis (2^{ry} Hemochromatosis)

* Beta thalassemia minor :- Causes a mild asymptomatic anemia with Hb level is 2-3g/dL below age-appropriate normal. Investigations $\rightarrow$ shows hypochromic & microcytosis with target cells.

By electrophoresis $\uparrow$ Hb A.

• No Rx is required

Note → Thalassemia is same as iron deficiency in microcytic hypochromic, but differ in :-

- (1) Thalassemia have reticulocytosis, while in IDA it's ↓ or zero.
- (2) RDW ↑ with Rx of IDA, while in thalassemia not.
- (3) Iron study is normal in thalassemia & abnormal in IDA.

Autoimmune hemolytic anemia [AIHA] ...

Def:- they are anemia resulting from ↑ RBC destruction due to RBC autoantibodies. IgM or IgG

Autoimmune hemolytic anemia is divided into warm or cold according to at what temperature the antibodies best cause hemolysis.

Epidemiology → more in middle aged females.

Etiology → (1) Idiopathic (most common cause).

(2) Autoimmune disease: (SLE, RA, IB ...)

(3) Neoplastic: ex → lymphoma, CLL, myeloma etc

(4) Drugs: ex → methyl dopa, penicillin, quinine, sulfa drug.

Note → Antibiotics as piperacillin & meronem can cause thrombocytopenia (Antibiotic induced thrombocytopenia) especially parenteral drugs. But infection itself can also ↓ platelets & RBC's count by causing DIC as complication.

(5) Infections: e.g → mycoplasma, EBV (causes cold type).

And all other causes are warm type → so warm type is more common than cold type.

Clinical picture :- Anemia + Jaundice

Cold type $\rightarrow$ Raynaud phenomena on exposure to cold.

starting pallor $\xrightarrow{\text{then}}$ cyanosis $\xrightarrow{\text{then}}$ Redness (reactive hyperemia)

Investigation :- ① CBC : normocytic, normochromic anemia or macrocytic hyperchromic $\rightarrow$ due to reticulocytosis.

② Blood Film : polychromasia, spherocytosis, Fragmentation (schistocytes) $\rightarrow$ Destroyed RBCs intravascular.

③ Direct antiglobin test (Coomb's test) : in both cold & warm AIHA is positive it's the definitive & diagnostic test.

Note $\rightarrow$ Leukemia + AIHA = CLL

Pneumonia + AIHA = mycoplasma.

Acute onset infection or common cold + lymphadenopathy + skin rash = EBV.

Treatment :- • Treat underlying cause

• Corticosteroids 80% responds and response may take 3 wks to occur)

• Splenectomy (if steroid didn't work). If steroid is working but slightly $\rightarrow$ $\uparrow$ dose of steroid and added azathioprine.

• Immunosuppression therapy For patients fails steroid or splenectomy can't performed $\rightarrow$ as low immune patients.

• Interferon & immunoglobulin therapy maybe helpful in cold type.

Note $\rightarrow$ Splenectomy is effective only with warm type ; because RBCs are destroyed inside the spleen. and have no role with cold type because hemolysis occurs intravascular.

Comparison

Type	warm 80% of cases	Cold 20% of cases
Site	Extravascular	Intravascular
Antibody	IgG	IgM
Active temperature	37 degree	4 degree

Respond to Rx

Steroid	Good	Poor
Splenectomy	Good	Poor
Warming	Not respond	Good

*** Differential Dx of microcytic hypochromic anemia:-

	Serum iron	Transferrin Saturation	Serum Ferritin	TIBC
Iron def. anemia	Low	Low	Low	↑
Anemia of chronic disease	Low	Normal	High	↓
Thalassemia	Normal	Normal	Normal	-
Sideroblastic anemia	High	High	High	↓
Lead poisoning	High	High	High	↓

Aplastic anemia:-

Def:- A pancytopenia associated with a hypoplastic B.M.

Etiology → A. Congenital e.g. autosomal recessive (Fanconi) anemia

B. Acquired:- 1. Idiopathic (most common cause).

2. Radiation. 3. Drug induced (gold, penicillamine, chloramphenicol, NSAIDs, carbamazepine, phenytoin & thyroid, azathioprine).

4. Viral infection (Parvovirus, hepatitis virus A, B & C, CMV & EBV).

5. Chronic benzene exposure.

* Clinical Features :-

May occur at any age. In either sex.

Onset rapid (over a few days) or slow (over weeks or months).

Symptoms and signs are caused by B.M Failure ($\downarrow$ RBC, $\downarrow$ WBC & $\downarrow$ PLT) $\Rightarrow$ anemia, recurrent infection & Bleeding.

* 1st presenting symptom usually is Recurrent infection due to $\downarrow$ WBC.

Liver, spleen & Lymph nodes are not enlarged; because stem cell receptors in all the body are not responding to erythropoietin, leukopoietin & thrombopoietin hormones $\rightarrow$ so no extramedullary hematopoiesis & no hepatosplenomegaly.

* Investigations :- Dx by exclusion.

✓ CBC : Anemia $\rightarrow$ normocytic or mildly macrocytic with a low or absent reticulocyte. Leukopenia & thrombocytopenia are usual.

✓ B.M examination (Diagnostic).

B.M is hypoplastic with increased fat (Fat/hemopoietic ratio 75% : 25%), remaining hemopoietic cells are normal appearance.

✓ There is no evidence of malignancy or megaloblastic changes.

✓ Megakaryocytes are particularly reduced.

Treatment :- • Supportive : blood transfusion & Prevention & Rx of infection.

• Immunosuppressive : Anti-lymphocyte globulin (ALG).

- Granulocyte colony stimulating Factor.
(↑ granulocyte, because the most common cause of death is neutropenic fever → neutrophils < 2500 .)
- Stem cell transplantation [Allogeneic transplant is successful in 80% of pts.]

Prognosis → Poor. $> 50\%$ die → because of infection.

D/D of pancytopenia :- ① B.M Failure :-

- Aplastic anemia, Megaloblastic anemia (Long standing).
 - Bone marrow infiltration by (acute leukemia, lymphoma, myeloma, myelodysplasia, solid tumor, T.B).
 - Myelofibrosis, Paroxysmal nocturnal hemoglobinuria, SLE.
- ② Increase peripheral destruction :- hypersplenism.

Pernicious anemia ...

It's the commonest cause of Vit. B₁₂ (cobalamine) deficiency.

- **Def:** A condition in which the portion of gastric mucosa that contains the parietal cells is destroyed through an autoimmune mechanism.

The parietal cells secrete intrinsic Factor, which is essential for cobalamine absorption.

Epidemiology: Age: usually after age 40.

Gender: more in females, white, colored eye.

More in persons of blood group A.

Clinical presentation :- Anemia GIT & Neurological symptoms + other Features include:

A. maybe associated with other autoimmune diseases
ex:- thyroid diseases, vitiligo, hyperparathyroidism, and Addison's disease.

B. It's associated with premature graying of hair or blue eyes and teeth problems.

C. ↑ risk of gastric cancer.

Investigations :- • Anti-parietal cell antibodies are positive in >90% but are found in 10% of normal people.

• Anti-intrinsic Factor antibodies are positive in 60% and are diagnostic.

patient may have anti-intrinsic Factor antibodies only.

Treatment ⇒ - Steroid.

- As Vit B₁₂ def. treatment.

high dose oral vit B₁₂ can be helpful in this case, if patient not tolerate parenteral route.

*** Hematological malignancies ***

* It's arise from a single cell (myeloid or lymphoid) in the B.M, thymus, peripheral lymphoid system.

Origin of leukemia from → B.M. & origin of lymphoma from → Lymph nodes.

* This cell undergoes a mutation leading to malignant transformation.

Transformed cells either proliferative excessively (Acute type) or resistant to apoptosis (Chronic type).

* Definition :-

① Leukemia's → Are malignant disorders of the hematopoietic stem cell, characterized by ↑ numbers of WBCs in the B.M and/or peripheral blood.

* Leukemia is classified by :-

Dominant cell type → myeloid, lymphoid.

Duration from onset to death → Acute leukemia (wks-months)
chronic leukemia (months-yrs).

* Acute leukemia → within a few months in most cases, and is associated with acute symptoms including severe anemia, Hemorrhage. (Bleeding is the 1st presentation symptom).

* Chronic leukemia → duration exceeds one year, with a gradual onset of symptoms of anemia.

② Lymphoma → It's a neoplastic proliferation of lymphoid cells originating in lymph nodes or other lymphoid tissue.

Classification of hematological malignancies...

(Lymphoid)

1. Acute lymphoblastic leukemia.
2. Chronic lymphocytic leukemia.
3. Non-Hodgkin lymphoma.
4. Hodgkin Lymphoma.
5. Multiple myeloma.

(Myeloid)

1. Acute myeloid leukemia
2. Chronic myeloid leukemia
3. Myeloproliferative disorders
(polycythemia, essential thrombocytosis, myelofibrosis)
4. Myelodysplasia (MDS)

* Etiology → Unknown, but several factors have been associated:-

- ① Genetic predisposition
 - Down's syndrome :- Certain inherited condition.
 - Fanconi's anemia :- conditions associated with defective DNA repair.
 - Ataxia telangiectasia :- Immune suppression.
 - Klinefelter's syndrome

② Infections → * Viruses : Epstein-Barr virus → Hodgkin's Lymphoma, Burkett's Lymphoma

Human T-cell leukemia virus (HTLV-1) → Adult T-cell leukemia / Lymphoma

HIV → high-grade B-cell lymphoma and brain lymphoma

* Bacteria : *Helicobacter pylori* (MALTOM) Gastric carcinoma

This type of malignancy Rx by Antibiotic (triple therapy) before chemotherapy

* Protozoa : Malaria → Burkett's Lymphoma

• Others: Ionizing radiation causes DNA mutation $\uparrow$ the risk of hematological neoplasm.

Toxins / chemicals ex: benzene predispose to Leukemia and Myelodysplasia (MDS).

Drugs: Alkylating agents / ex: mephalan, mustine, cyclophosphamide predispose to AML and MDS.

Acute Leukemia :-

Def:- Acute leukemia is a malignant disorder in which hemopoietic blast cells constitute $>20\%$ of B.M cells.

• The primitive cells usually also accumulate in the :-

① Blood ② Infiltrate other tissues. ③ Causes B.M Failure

• 1st myeloblast infiltrate B.M (immature cells) $\rightarrow$ then will lead also to failure of maturation of thromboplast & erythroblast $\rightarrow$ causing Pancytopenia, then by $\uparrow$ of intramedullary pressure $\rightarrow$ some of myeloblastic cells will escape to the peripheral blood & deposit inside the organs.

• Lymphoblastic cells are smaller in size than myeloblast & have less cytoplasm, so when escape from the B.M ^{can} penetrate any barrier inside the body as BBB & causing more rapid metastasis while myeloblast is larger in size $\rightarrow$ difficult to penetrate. Lymphoblastic also cause more lymphadenopathy & have a high recurrent rate $\rightarrow$ That's why the Rx of acute lymphoblastic is more difficult (Induction, consolidation, Maintenance). Maintenance phase $\rightarrow$ to prevent recurrent rate.

- B.M. transplantation successful rate is excellent below age of 30 yrs old, equal or good at age 30-50 yrs, poor at age 50-60 yrs & contraindicated above 60 yrs old.

symptoms of acute leukemia (Both types):

Starting by → (1) B.M. Failure (pancytopenia) → Bleeding is the most common presentation

then → (2) Peripheral spread or infiltration

& lastly → (3) FAHM (constitutional) symptoms

- Fever usually is 2nd to infection (opportunistic).

Case → patient 10 yrs old complaining of recurrent epistaxis, his CBC investigation in every visit shows 2nd platelets count normal or low, WBC → Normal, RBC → low & pt have also recurrent infection, bleeding & anemia.

This case → Aleukemic leukemia.

Normal WBC count in CBC doesn't exclude leukemia.

Types

(AML)

(ALL)

- | | | |
|----------------|--|---|
| → Definition | • It's failure of cell proliferation (maturation arrest), ↑ blast cells. | • It's failure of cell death (apoptosis) → number of mature cell increased. |
| → Cells | • Myoblast as neutrophils & eosinophils. | • Lymphoblast & B-lymphocyte mainly or T-lymphocyte. |
| → Epidemiology | • Male > Female
Age → > 50 yrs (adult). | • Male > Female
Age → 1-5 yrs.
Commonest leukemia in children. (B.M. transplant is benefit option). |

Types	AML	ALL
Size	Large	Small
Nucleus	Multiple	Single or double
Cytoplasm	Abundant	Scanty
Myeloperoxidase	+ve	-ve
Sudan stain	+ve	-ve
Per stain	-ve	+ve

Morphological differences

Cyto-chemistry

Clinical

• Rapid short history < 3 months

Pictures

1. B-M Failure :- Anemia, Bleeding, Infection

2. Feature due to tissue infiltration :-

- equal in severity in both types
- Bone & joint pain in both types.
 - Hepatosplenomegally in both types (But more in ALL).
 - Lymphadenopathy occurs more in ALL.
 - Salivary gland enlargement (parotid) ALL.
 - Infiltration in meninges and testes occur in ALL.
 - Infiltration in Gums occurs in AML M4,5 (Gum hypertrophy).
 - DIC occur in AML especially in M3 stage.
3. Constitutional symptoms :-
Fever usually due to infection, anorexia, malaise.

Note → Elevated WBCs could be 2nd to leukemoid reaction not leukemia; differentiated by → ALP inside WBCs is ↑ in leukemoid (Functional WBCs) + ↑ PLT but in leukemia ALP & PLT count are ↓ (Low)

ALL

Types

AML

Investigations

Lab $\Rightarrow$ may $\uparrow$ uric acid & $\uparrow$ LDH, $\uparrow$ K^+ $\rightarrow$ Tumor lysis syndrome
 $\uparrow$ PO_4^{3-} , $\downarrow$ Ca^{2+} . (due to destruction of malignant

cells by chemotherapy.

• $\uparrow$ uric acid $\rightarrow$ 1st thing occurs & can lead to renal failure or gout

prevented by $\rightarrow$ IV-Fluid then allopurinol drug before giving of chemotherapy

• $\uparrow$ K^+ $\rightarrow$ 2nd thing occurs & leading to arrhythmia which's the most common cause of death by chemotherapy. Prevented by $\rightarrow$ Ca^{2+} gluconate

Blood Film $\Rightarrow$ show blast cells

Auer rods pathognomonic for AML (M3)

B.M examination $\Rightarrow$ show blast cells $> 20\%$ (normal $< 5\%$).

Note $\Rightarrow$ usually acute leukemia $> 50,000$, chronic leukemia $> 100,000$ WBC's count. & in chronic leukemia WBC's never to be normal.

Treatment 1. Induction of remission

1. Induction of remission

2. Consolidation

2. Consolidation

Induction phase destruct nearly

3. Maintenance

90% of malignant cells, while consolidation destruct 10%.

At home $\rightarrow$ For years (prevent recurrence).

Note $\Rightarrow$ By early detection acute leukemia & lymphoma can be curable.

French - American - British (FAB) classification of acute

Leukemia :- "Acute Myeloblastic leukemia"

M₀ → Undifferentiated by morphology + cytochemistry

M₁ → Little differentiation > 90% blasts

M₂ → Differentiated 30-90% blasts

*** M₃ → Promyelocytic highly granular (Auer rods)

auer
rods



The best prognosis because responding well to All-trans retinoic acid (ATRA)



M₄ → Myelomonocytic

M₅ → Monocytic differentiation

M₆ → Erythroid differentiation

M₇ → Megakaryoblastic

"Acute Lymphoblastic leukemia"

According to cell morphology :-

L₁ small cells, high nuclear / cytoplasm ratio

L₂ larger cells, low nuclear / cytoplasm ratio

L₃ Vacuolated, basophilic blast cells, bad prognosis

According to immunophenotype :-

T-cell phenotype 25%

B-cell phenotype 5%

Pre-B-cell phenotype 70%

} → Poor prognosis

• All subtypes have > 20% blast cells in the B.M.

• Treatment → 1 Supportive :-

1. Blood transfusion or packed RBC to keep Hb > 10 g/dl.
2. Plt transfusion to keep Plt $> 100,000$.
3. Treatment of infection. (broad spectrum antibiotic, antiviral (acyclovir), antifungal (amphotericin))
management of neutropenic fever → do full septic screen from any sputum & urine → & send for C&S.
then give broad spectrum antibiotic & antipseudomonas
→ if fever at 3rd day of Rx still high → give antiviral drug → if still rising at 5th day → give antifungal.
but fever is usually response after 72 hr.
4. Allopurinol & IV fluid to prevent uric acid → RF (complication of tumor lysis syndrome).
5. Leukopheresis → to treat leukostasis (which's stasis of blood 2nd to very high WBCs).
6. Psychological support.

- The difference between cytogenetic & hematological remission is when most of malignant cells are killed & destructed in the body in induction phase → this's called hematological remission but when the original mutated cells are also killed → this's called cytogenetic remission (need long time & high dose of Rx).
 - Cytogenetic remission should do it before stem cell transplant.
 - 2 Chemotherapy :- Aim of treatment is to destroy leukemic cells without damaging normal stem cell.
- There are 3 phases of Rx in ALL & 2 phases in AML.

1. Remission induction (AML & ALL)

Aims to destroy most of malignant cell by combination of chemotherapy. (hospital) short duration 6wk with high dose

2. Remission consolidation (AML & ALL)

Residual malignant cells are attacked by consolidation therapy (hospital) long duration (8wks - 3months) with low dose

3. Remission maintenance

For ALL (not AML) → because AML have low recurrence rate & is given at home. Long duration (2-3yrs) with low dose

If patient relapse after hematological remission → The disease will be more aggressive & more resistant to chemotherapy regime → in this case the aim is change to cytogenic remission (high dose, long period) for destroying all malignant stem cells, the do → stem cells transplant.

* **Remission induction** :- AML → Daunorubicin (Doxorubicin) + Cytarabine

ALL → Vincristine + Prednisolone + L-asparaginase + Daunorubicin + Methotrexate (intrathecal).

* **Remission consolidation** :- a number of cycles of intensive chemotherapy with each course requires 4-6wks in hospital.

Note → intrathecal methotrexate is given for all ALL patients but craniospinal irradiation is given only for brain involved pts.

Stem cell transplantation may be used in patient age < 55 years.

- **Remission maintenance** :- Less intensive chemotherapy repeating cycles for 2-3 yrs is used maintain remission in ALL (not AML) and is given at home.
- Note → Alternative chemotherapy as (Hydroxyurea or mercaptopurine) can restrict WBC proliferation.
- Important differences between the Rx of ALL and AML:
 1. In ALL → CNS is usually involved and systemic chemotherapy can't cross Blood-brain-barrier.
Therefore prophylactic cranial irradiation + high dose methotrexate (Intrathecal or omaya reservoir).
 2. In AML M3 → All Trans retinoic acid (ATRA) is given to induce differentiation.
 - 3 **Radiation therapy** :- Can be used as adjunctive therapy with chemotherapy to :-
 - ① Decrease pressure symptoms → to ↓ size of cancer effects.
 - ② In CNS involvement & bone involvement.
 - 4 **Bone marrow transplant** :- Attempt in patients below 60 yrs and best age below 30 yrs.
After cyto-genic remission to decrease recurrence and failure.
Hematological remission → destroy 30% to 95% of peripheral malignant cells.
Cytogenetic remission → Kill the originated cells (stem cell) of malignancy.

- 5 Immune therapy = ✓ Injection of BCG vaccine.
This method → Failed, but may be useful in Rx of transitional cell carcinoma of urinary bladder.
- ✓ Allogenic external leukemic cells radiation.
- ✓ Injection of monoclonal antibody (Rituximab).
but it's very effective only in Lymphoma.
- Prognosis → without therapy the median survival of pts acute leukemia is about 5 wks.
- 80% of pts < 60 yrs. with ALL or AML achieve remission.
- 40% > 60 yrs.
- In AML Promyelocytic [M3] has a good prognosis.

Prognosis of ALL

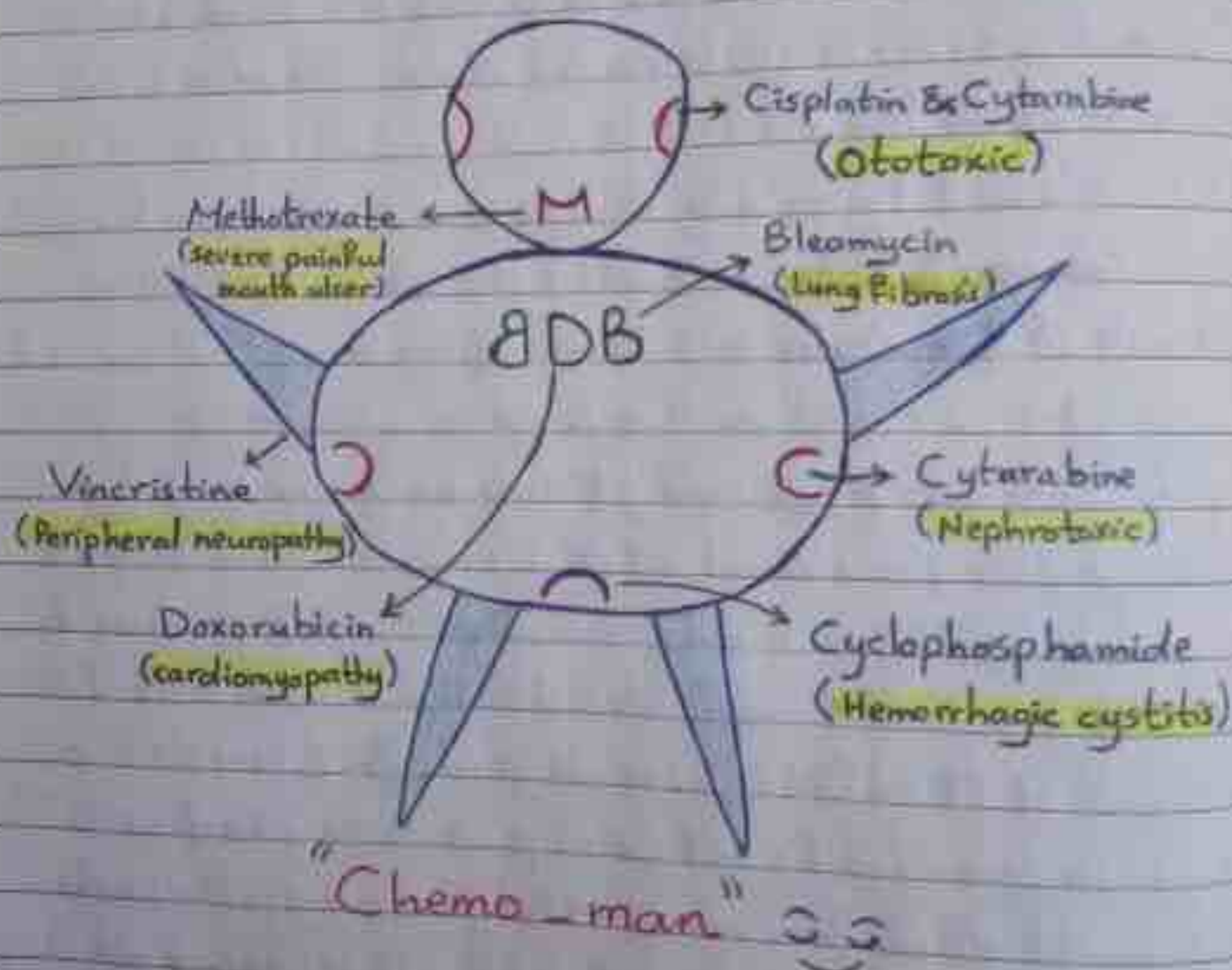
Factors	Favorable (good prognosis)	Unfavorable (poor prognosis)
Age	2 - 10 yrs	< 2 → > 10 yrs
Sex	Female	Male
Race	White	Black
WBC count	< 50,000	> 50,000
Organ involve	None	CNS involvement
Chromosomal defect	None	Philadelphia Translocation (9:12)
Immune phenotype	L1 & Pre B type	B & T type & L2

Note → when CML transformed to ALL on top of Philadelphia translocation (chromosomal mutation) → it's poor prognosis.

Other poor prognostic Factors for both :-
 Anemia, thrombocytopenia, organomegally, Failure to
 remission or rapid relapse, Mo-M5-M6-M7 in AML

S/E of chemotherapy in general:-

Hair loss, B.M depression, bone pain, psychological depression



Note → patient on "doxorubicin" chemotherapy should do
 Echo before use of drug & every 6 months after starting
 use of drug.

Chronic myeloid leukemia ---

- **Def:-** This's myeloproliferative disorder characterized by an increase in neutrophils and their precursors in the peripheral blood.
- **Mechanism:** ↓ apoptosis of myeloid lymphocyte → peripheral blood will be full with mature cells but non functional & B.M is normal → so in chronic leukemia cellular infiltration occurs 1st in peripheral blood.
These cells will ↑ gradually on long term & WBC count may reach 600,000 → these cells will ↑ the viscosity of blood & ↑ risk of thrombosis & occlusion → priapism.
- ↑↑ myelocytes → deposit in liver & spleen → severe huge hepatosplenomegally & usually there's no lymphadenopathy. while lymphocytes deposit in L.N, leading to → massive severe lymphadenopathy with mild to moderate hepatosplenomegally. After long time of ↑ non functional cells → will deposit also in the B.M (B.M Failure → occurs gradually & late).
- Huge organomegally will cause pressure symptoms as abdominal discomfort, early satiety, regurgitation ... etc. After long time of splenomegally → hypersplenism (↑ destructive function) → then B.M will compensate by ↑ immature WBC's (blast cells).
This will transform chronic phase to → Accelerated phase & once myelocytes become more than 20% → it's acute leukemia.

- CLL can't transform to acute leukemia, because malignant cells deposit in the L.Ns, and spleen not enlarged massively $\rightarrow$ so no hypersplenism, no blastic crisis phase & no acute leukemia $\rightarrow$ but can transform to lymphoma.

• Philadelphia chromosome :-

This chromosome is present in more than 95% of pts. with CML (good prognosis if present in CML).

Philadelphia chromosome results due to translocation b/w long arm of chromosome 9 & 22.

Result in BCR ABL Fusion gene which codes for a protein $\rightarrow$ increased tyrosine Kinase activity, (which inhibits cell death, $\downarrow$ apoptosis)

The Philadelphia chromosome may occur in ALL, but its bad prognosis if present

Natural history $\rightarrow$ the disease has 3 phases

① Chronic phase : pts is responsive to Rx & disease is controlled. ($\uparrow$ Platelet count) this lasts 3-5 yrs.

② Accelerated phase : (not in all pts) disease becomes difficult to control, there is marked by anemia & Platelet count Falls, blast cells $> 5\%$ in blood & $> 20\%$ in BM, unexplained Fever.

③ Blast crisis : disease transforms to acute leukemia (AML in 70% & ALL in 30% of pts). This leukemia resists treatment & survival is often < 4 months.

- * Treatment $\Rightarrow$ ① Treatment of chronic phase :-
 - **Imatinib** $\Rightarrow$ the first line of treatment, it's an inhibitor of the tyrosine Kinase (improve the prognosis & $\downarrow$ requirement of B.M transplant).
it results in complete hematologic remission of $>90\%$ and cytogenic remission in 76% .
it's best to transplant patients in complete remission.
 - * Hydroxyurea & alpha-interferon (IFN) will control the raised WBCs count. (not used anymore).
Busulfan, its use has been replaced by IFN-alpha and/or hydroxyurea. but it's carcinogenic $\rightarrow$ not used anymore).
 - * Splenectomy is not effective, because hypersplenism doesn't occur yet, but once patient have aplastic crisis do splenectomy.
 - * Radioactive isotope chromium: used to differentiate b/w pancytopenia due to hypersplenism & other causes as S/E of chemotherapy. it's visualize hyperfunctional spleen $\rightarrow$ (+ve in hypersplenism).
 - ② Accelerated phase :- Imatinib + Hydroxyurea + Splenectomy in case of hypersplenism.
 - ③ Blast crisis phase :- As for acute leukemia.
- Prognosis of CML : Median survival is about 4 years.
- 1 Philadelphia chromosome -ve pts $\rightarrow$ have poor prognosis.
[median survival of $<1\text{yr}$].

2. Resistant to imatinib.
2. Anaemia.
2. Old age.

Chronic lymphocytic leukemia ...

Def (CLL) is a B-cell clonal lymphoproliferative disease in which lymphocytes accumulate in the blood, bone marrow and often in the L.N & spleen (lymphocyte count > 5000).

- **Mechanism** → lymphoproliferation ($\uparrow\uparrow$ lymphocytes in the peripheral blood → severe lymphadenopathy leading to compression symptoms → ① over the mediastinum (cough, dyspnea, SVC obstruction → etc.), ② para-aortic L.N compress over biliary system → obstructive jaundice & can compress over pelvis leading to L.L elephantiasis like edema. Abnormal B cell release → Abnormal plasma cells, which will release abnormal antibodies.

These antibodies causing AIHA warm type & may be associated with autoimmune thrombocytopenia → Evan's syndrome.

- so the result is → ① pressure symptoms by lymphadenopathy
- ② $\downarrow$ Ig & immunity → recurrent infection (the cause of death in CLL patient).
- ③ Autoimmune disease involved RBCs & PLTs.

• Clinical staging for CLL :-

Stage A $\Rightarrow$ No anemia or thrombocytopenia + < 3 areas of lymphoid enlargement $\Rightarrow$ No treatment

Stage B $\Rightarrow$ No anemia or thrombocytopenia + > 3 areas of lymphoid enlargement $\Rightarrow$ Need treatment

Stage C $\Rightarrow$ Anemia or / and thrombocytopenia $\Rightarrow$ Need Rx

Rx of stage B & C :-

• Chlorambucil $\rightarrow$ to C $\downarrow$ lymphocyte count & $\downarrow$ L.N & Spleen size).

• Fludarabine $\rightarrow$ May be used either alone or in combination.

Corticosteroids for BM Failure or autoimmune hemolytic anemia or thrombocytopenia.

Splenectomy may improve low blood counts due to hypersplenism.

Supportive treatment : as before.

• Complications of CLL :-

1. Hypogammaglobulinaemia $\rightarrow$ leading to bacterial and viral recurrent infections.

2. Warm autoimmune hemolytic anemia in 10-15% of patient

3. Transformation to high grade lymphoma (Richter's transformation) $\rightarrow$ which's poor prognosis, not to acute leukemia as (CML).

• Prognosis :- 50% of pts die due to infection.
30% of cause unrelated to CLL.

The median survival is 5-6 yrs.

CLL rarely progresses to acute leukemia.

CLL

Types

CML

Definition

• It's Failure of cell death (apoptosis) → number of mature cell increase

Cell

• Neutrophils

• Lymphocytes

Epidemiology

Male > Female

Male > Female

Age: 33-55 yrs.

Age: > 65 yrs.

commonest leukemia in adult

Clinical picture

May be asymptomatic

most pts asymptomatic

✓ Constitutional sympt.

✓ Night sweats & Fevers

✓ Symptom of anemia

uncommon & should

(anemia of illness).

evaluation for infection

✓ Sternal tenderness.

✓ Marked lymphadenopathy

✓ Massive splenomegally.

✓ Moderate splenomegally

(pain in lt hypochondria, early satiety).

✓ Hepatomegally uncommon

✓ hepatomegally in 50%

hemolytic anemia

of pts & no lymphadenopathy

and autoimmune

✓ Pseudopapism, visual disturbance

thrombocytopenia.

& headache due to

hyperviscosity.

Investigations

Lab

↑ uric acid & ↑ LDH, ↑ B₁₂

Low immunoglobulin

(↑ B₁₂ due to malignant

neutrophils secrete abnormal

excessive production of transcobalamin I)

Types

CML

CLL

Lab

- ↓ leukocyte alkaline phosphatase

CBC

- ↓ Hb, ↑ PLT (because CML is part of myeloproliferative diseases, have JAK 2 mutation & can transformed to each other).

- WBC always ↑↑ often > 50,000. (mainly neutrophils) (Basophilia).

B.M examination

- blast cells < 10%

- blast cells < 10%

chromosomal → Philadelphia chromosome +ve
(9-22 BCR/ABL)

Immune type →

B-cell (CD19, CD23 +ve)

T-cell (CD5 +ve).

Treatment

- Imatinib

- chlorambucil +
Fludarabine

- cortisone and
splenectomy for
autoimmune hemolysis

Myeloproliferative disorders

- **Def:-** The myeloproliferative disorders are a group of four diseases caused by clonal proliferation $\rightarrow$ neoplastic of hemopoietic stem cell, due to abnormality in chromosome 9 position 516 by substitution of valine a.a by another a.a results to JAK2 mutation.

• Myeloproliferative disorders are:-

1. WBC $\rightarrow$ Myeloid leukemia.
2. RBC $\rightarrow$ Polycythemia rubra vera.
3. Platelets $\rightarrow$ Essential thrombocytosis.
4. Fibroblast $\rightarrow$ Myelofibrosis.

Note $\rightarrow$ JAK2 mutation is in 95% of polycythemia rubra vera pts & is in 50% of Essential thrombocytosis & myelofibrosis pts & variable in Myeloid leukemia pts.

There often transformation from one to another & can be associated to each other (combined).

• **General notes about myeloproliferative diseases:-**

1. We can differentiate between leukemia & leukemoid reaction by ALP + Genetic study (Philadelphia chromosome & JAK2 mutation) because polycythemia rubra vera may $\uparrow$ WBCs count to 30-40,000 with $\uparrow$ ALP as leukemoid reaction.
2. Hydroxyurea & Interferon are effective Rx for all myeloproliferative diseases + supportive Rx.
3. In myelofibrosis disease, there's an increase in megakaryocytes $\rightarrow$ $\uparrow$ Platelet derived growth factor $\rightarrow$ stimulate Fibroblast in BM & cause BM Fibrosis.

Functional megakaryocytes will lead to thrombosis, & non functional megakaryocytes will lead to bleeding.

4. Mortality rate is higher by thrombosis and it's leading events as stroke, IHD, Pulm. edema etc

that's why aspirin can be used with all myeloproliferative diseases especially essential thrombocythosis & myelofibrosis

5. IV radiophosphorus cause B.M suppression, but effective for elderly patient only because in children → transform myelofibrosis to acute leukemia.

B.M transplant effective more in children.

6. The 4 types of myeloproliferative diseases carrying → poor prognosis, except polycythemia rubra vera if presented without association with other types of diseases & not transformed (isolated) → patient can survive for yrs. (about 15 years)

Myelofibrosis ...

Def:- Gradual progressive replacement of normal B.M by fibrous tissue

Pathophysiology:- gradual B.M fibrosis → escape of large number of stem cells to liver & spleen → Extramedullary hematopoiesis (leukoerythroblastic changes) → B.M release tear drop RBCs b/w fibrous tissue.

• Massive splenomegally + leukoerythroblastic changes + Tear drop RBCs → Myelofibrosis.

- Extramedullary hematopoiesis of liver & spleen + some cells released by B.M $\Rightarrow$ $\uparrow\uparrow$ hypercellular in peripheral blood $\rightarrow$ after long time $\rightarrow$ spleen become hypersplenism & destroy many cells $\rightarrow$ change from hypercellular to pancytopenia.

Clinical picture :- 1. Abdominal distension & abdominal pain due to organomegaly (massive splenomegally).

2. symptoms of anemia, recurrent infection & bleeding due to pancytopenia.

3. Systemic symptoms ex: wt loss, fever & night sweating.

- * Investigations :- CBC $\Rightarrow$ Anemia, $\uparrow$ WBC & $\uparrow$ Plt early in the disease. (pancytopenia in late stage).

Blood Film $\Rightarrow$ Immature WBC, & RBCs (leukoerythroblastic changes with red cells are shaped like teardrops and giant platelets may be seen).

B.M examination $\Rightarrow$ Aspiration: Dry tap.

Biopsy: hypercellular B.M with extensive fibrosis.

- * Treatment :- 1. Supportive Rx, folic acid supplement.

2. Hydroxyurea & Interferon.

3. Aspirin if indicated.

4. I.V. radiophosphorus for old patients.

B.M transplant for young pt.

5. Splenectomy for hypersplenism.

Note $\Rightarrow$ This disease can proliferate to other types of myeloproliferative disease or to acute leukemia.

Polycythemia ---

Def:- It's an increase in hemoglobin concentration above normal.
It may be true or spurious.

True polycythemia $\rightarrow$ exists when the total red cell mass (RCM) is increased above normal.

RCM normally $< 15\%$, $> 25\% \rightarrow$ True polycythemia.

Spurious (pseudo or stress) $\rightarrow$ polycythemia exists when an elevated hemoglobin concentration is caused by a reduction in plasma volume (dehydration).

Etiology:- * True polycythemia:

1. Primary $\rightarrow$ Polycythemia rubra vera.

2. Secondary $\rightarrow$ Erythropoietin appropriately (2^{nd} to hypoxia) increased:- High altitude, Smoking, Cyanotic congenital heart disease, Chronic lung disease (COPD, obstructive sleep apnea).

$\rightarrow$ Erythropoietin inappropriately (without hypoxia) increased:

Renal disease: Renal cell CA, renal cyst, hydronephrosis.

Tumors: Uterine Fibroid, hepatocellular CA & bud chiri syndrome, cerebellar hemangioma, lung cancer.

(Bronchogenic carcinoma).

* Relative (spurious) polycythemia:

Plasma volume depletion (ex: Diuretic therapy, Dehydration).

Stress (Pseudo-polycythemia).

Polycythemia rubra vera (PRV)

Def:- myeloproliferative disorder caused by clonal abnormal excessive proliferation of a marrow stem cell leading to an $\uparrow$ in red cell volume $\pm$ $\uparrow$ granulocytes & Platelets.

Epidemiology: Age > 40 yrs, male $\approx$ Female.

Genetic $\rightarrow$ mutation in JAK2 is present in approximately 95%.

* In PRV $\rightarrow$ RBCs can proliferate & mature in vitro without added erythropoietin.

Clinical pictures: 1. Plethoric appearance and conjunctiva suffusion + palmar erythema.

Note $\rightarrow$ when there's red eye, conjunctivitis or glaucoma, don't depends on conjunctiva to examine signs of anemia.

2. Erythromelalgia $\rightarrow$ it's hyperemic and inflamed extremity common in PRV.

Note $\rightarrow$ cyanosis easy to develop in case of polycythemia.

(Pain + cyanosis in extremities due to deoxy Hb).

3. Pruritis, typically after a hot bath due to $\uparrow$ histamine level (by H_1).

& Peptic ulcer because $\uparrow$ WBCs release high level of histamine which will stimulate parietal cell to release high level of HCl.

4. Hyperviscosity may lead to chronic headache & visual disturbance, vertigo, tinnitus, $\downarrow$ concentration, $\downarrow$ memory.

5. Abnormal platelets function $\rightarrow$ if functional will lead to thrombosis (DVT, stroke, IHD, bud chavir syndrome, ischemic mesenteric artery $\rightarrow$ Abdominal pain).

if non functional $\rightarrow$ Hemorrhage.

6. Enlarged spleen is found in 75% of pts (NOT found in other causes of polycythemia).

7. Hypertension in a $\frac{1}{3}$ of pts. "uncontrolled" $\rightarrow$ patient complain of recurrent attacks of headache + Blurred vision.

* Investigations :- 1. CBC $\rightarrow$ $\uparrow$ Hct, $\uparrow$ Hb, $\uparrow$ RBC and $\uparrow$ RCM by radioisotope scan.

$\rightarrow$ 75% of pts have $\uparrow$ WBCs = Functional + $\uparrow$ Platelets.

Note $\rightarrow$ The only malignancy have $\uparrow$ ALP.

JAK2 mutation +ve in 95% of pts.

2. Blood test $\rightarrow$ Neutrophil alkaline phosphatase (NAP) is raised and ESR is low.

The erythropoietin level is low or normal ($\uparrow$ RBCs synthesis inhibit erythropoietin release from Kidney & liver).

3. Iron store $\rightarrow$ decrease or absent.

Note $\rightarrow$ 2nd polycythemia $\rightarrow$ there's hypoxemia $\rightarrow$ Kidney release high level of erythropoietin $\uparrow$.

In this type there's no splenomegaly, normal WBCs count & Platelets & there's no depletion in iron store.

* Treatment :- As Rx of Myelofibrosis + regular venesection used to $\downarrow$ hyperviscosity.

* Causes of abdominal pain in polycythemia rubra vera :-

- 1) Peptic ulcer
- 2) Budd-chiari syndrome
- 3) Mesenteric ischemia

Essential thrombocythosis

Def:- It's a malignant proliferation of megakaryocytes
 ~ Persistent elevation of the blood platelet count usually
 with plat. count > 1 million/ml in absence of 2nd cause.
 Pt around 60 years and present with thrombosis or
 hemorrhage, depending on whether the platelets are
 functional or not.

Note ~ Purpura of essential thrombocythosis is flat - not raised.

1st thrombocythosis can be isolated or combined.

2nd thrombocythosis usually b/w 450 - 1,00,000 & often benign

causes of 2nd thrombocythosis could be:-

1. IDA.
2. Hemorrhage pre & post op.
3. Stress
4. RTA.
5. Trauma
6. post splenectomy
7. Infection & Inflammation.

• **Investigations:-** CBC $\rightarrow$ Plat. count > 1 million, with normal RBCs
 & WBCs $\rightarrow$ if also elevated think of PRV or CML

B.M $\rightarrow$ proliferation of megakaryocytes

PCR $\rightarrow$ Positive mutation JAK 2 in 50% of cases

Iron study $\rightarrow$ 1st (essential) thrombocythosis should be normal

2nd thrombosis $\rightarrow$ usually $\downarrow$ especially due to IDA or could be
 $\downarrow$ if associated with polycythemia rubra vera

• **Treatment:-** Asymptomatic pts with count < 1 million &
 there's no thrombosis $\rightarrow$ observation + aspirin

Symptomatic pts or count > 1 million or there's thrombosis
 $\rightarrow$ hydroxyurea + aspirin + interferon, IV radiophosphorus

• Plt pheresis $\rightarrow$ used in acute phase (acute response)

Lymphoma

Def:- neoplastic proliferation of lymphoid cells originating in lymph nodes or other lymphoid tissue (spleen or mucosa-associated lymphatic tissue)

- Notes:-
 - * Generalized Lymphadenopathy means 2 groups of L.N. are enlarged.
ex: Cervical + axillary & should be pathological.
 - * Pathological L.N. enlargement $\rightarrow$ Cervical $> 1\text{cm}$ & palpable
Inguinal $> 2\text{cm}$, supraclavicular $\rightarrow$ if just palpable or slightly enlarged $\rightarrow$ it's pathological.
 - * Any infection affecting specific part of the body $\rightarrow$ can lead to enlargement of L.N. of this part.
ex: pharyngitis, tonsillitis or dental caries lead to cervical L.N. enlargement (Most common cause of cervical lymphadenopathy).
 - * Every L.N. enlarged by infection can spread & causing enlargement of neighboring L.N. (contagious spread).
ex: Cervical $\rightarrow$ axillary $\rightarrow$ Mediastinum.
 - * Some of malignancies spread contagiously & some of them spread randomly.
 - * Lymphoma in general it's good prognosis & can be cure.
 - * No need to take A.M. biopsy from lymphoma pt, except for detect the complication.
- B-cell lymphocyte is large in size & has slow rate of spread (delay) & it's well respond to chemotherapy while T-lymphocyte is smaller & spread more rapid.

& resist to chemotherapy & radiotherapy, also the onset of aged T-lymphocytic tumor is old age usually.
So T-lymphocyte carry poor prognosis than B-lymphocyte.

* Epidemiology:-

(Hodgkin Lymphoma)

Gender: more in males.

Bimodal distribution with
major peak b/w (20-30 yrs)

& minor peak at 60yrs.

(Non Hodgkin Lymphoma)

more in males.

more in elderly >60yrs

Etiology:- The cause is unknown & both types have Familial Hx.

(Hodgkin Lymphoma)

- * Wood worker.
- * High educated individuals.
- * High socioeconomic state.

(Non Hodgkin Lymphoma)

- * EBV & malaria in → Burkett's Lymphoma.
- * Helicobacter pylori.
- * Drugs (ex: phenytoin).
- * Autoimmune disease :- ex: Sjogren's syndrome (↑ risk 40 times).
- * Immune deficiency as AIDS.

Notes → Extranodal diffuse spreading more with non-Hodgkin lymphoma than Hodgkin Lymphoma.

Histological classification of Lymphoma

Hodgkin Lymphoma

(Reed-sternberg cell present)

{الخلية}



large cell with

double nucleus

(PS) cell are characteristic and

are of $\rightarrow$ B-cell origin

• Histological subtypes (Raj classification):

1. Classical types:-

A. Nodular Sclerosing HL:

most common (70%), young
Female. Mediastinal disease
may occur. good prognosis.

B. Mixed cellularity HL

C. Lymphocyte rich classical HL

D. Lymphocyte depleted HL

B, C, D $\rightarrow$ Poor prognosis

2. Non classical:- Nodular
Lymphocytic predominant 5%
(The best prognosis)

Non-Hodgkin lymphoma

(Reed-sternberg cell absent)

{الخلية}

B T T B T $\rightarrow$ 70%

T B B T B $\rightarrow$ 30%

T T B T T

O O O O O

Small cells (mixed), if

T-cell is predominant

$\rightarrow$ T-cell in origin & vice versa.

NHL > 70% are B-cells &

30% are T-cell. there are

2 histological categories:

• Low grade NHL:-

Divided slowly, presented

late, resistant to Rx

survival maybe prolonged
10 yrs

• High grade NHL:-

Divided rapidly & metastasized
early $\rightarrow$ so presented early

Radiation & chemo sensitive but
carries higher early mortality
rate survival per months

Notes:- B-cell in origin lymphoma (non-Hodgkin) is worse prognosis than B-cell Hodgkin type.

- Most common presentation of lymphoma is cervical painless lymphadenopathy - but could be painful when patient drink alcohol $\rightarrow$ in early stage it's scattered then matted (late)
- Hodgkin lymphoma (spread contagiously), Non Hodgkin (spread randomly)
- Immunotherapy can transform lymphoma from Hodgkin to non Hodgkin type $\rightarrow$ ex: cyclosporine in case of renal transplant to $\downarrow$ incidence of rejection.

Clinical Feature	Hodgkin	Non Hodgkin
Prevalence	• less common	• More common
Age	• Bimodal (25, 60)	• 65-70
Common Location	• cervical, supraclav. axillary, mediastinum, para aortic, inguinal	• supraclavicular, Abdominal cavity (Randomly)
Extranodal tissue	• + doesn't change the stage & treatment	• + doesn't change stage & treatment

Extranodal systemic

1. GIT	+	++
2. Cardio	+	++
3. Neuro	+	++
4. B.M	++	++
5. Bone	rare	rare

Note $\rightarrow$ Lymphoma usually doesn't metastasize to the bone, invading B.M $\rightarrow$ Bone pain

Notes $\Rightarrow$ Nodular sclerosing type of Hodgkin lymphoma is the most common one causing mediastinal lymphadenopathy but the most common subtype of lymphoma that lead to SVC obstruction is non Hodgkin.

- L.N. enlargement lead to inflammation in the surrounding tissue (locally) $\rightarrow$ it's called extranodal tissue but when spread systemically by blood, it's called extranodal systemic $\rightarrow$ important for staging & decision of Rx.
- Characteristics of L.N. enlargement: multiple enlarged, painless, separated, mobile, rubbery in consistency, not attached to skin or underlying structure.
- Lymphoma bulky disease $\rightarrow$ 1 or 2 L.N. enlarged ≥ 10 cm in pt with lymphoma (by CT or PET scan).
- Persistent L.N. enlargement > 3 months & it's pathological, rubbery in consistency & painless $\rightarrow$ should take biopsy to exclude lymphoma.
- The most common extranodal involvement is stomach.

Investigation :- • Hodgkin :-

- (1) Blood tests :- (i) CBC $\rightarrow$ anemia (normocytic normochromic)
CBC is one of investigations that determine prognosis of lymphoma.
 - (2) $\uparrow$ ESR, $\uparrow$ uric acid.
 - (3) $\uparrow$ LDH $\rightarrow$ useful as prognostic marker and for monitoring response.
 - (4) B₂ microglobulin $\rightarrow$ produced by B lymphocyte $\rightarrow$ indicate poor prognosis.
- All blood tests indicate poor prognosis & need longer cycles of chemotherapy.

② RFT, LFT, RBS.

③ Radiology staging: by CT or PET scan.

④ B.M aspiration & Biopsy.

* Non Hodgkin :- In addition to that changes seen in HL may cause :-

Pancytopenia because of B.M Failure.

Para protein IgG & IgM may rise.

In both Dx by L.N biopsy.

* B-symptoms of Lymphoma (indicated for chemotherapy)

① Wt Loss $\rightarrow$ 10%, non intentional in last 6 months.

② Fever (Pel Ebstein Fever).

③ Drench sweating $\rightarrow$ severe enough to change the clothes.

Pruritis is a common symptom in lymphoma but it's not considering as B-symptom (doesn't change the stage & doesn't affect the Rx).

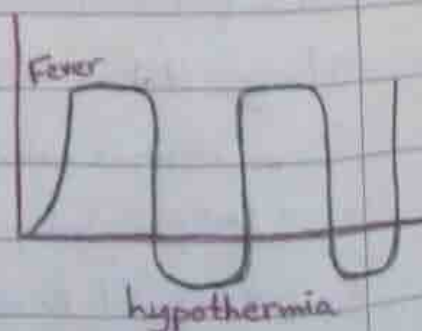
D/D of pruritis in hematological diseases :-

1- Leukemia.

2- Lymphoma.

3- PCRV.

4- IDA.



Notes $\Rightarrow$ Anemia & thrombocytopenia are not present unless lymphoma invade the B.M.

* B.M aspiration is not indicated for Dx in case of lymphoma unless there's unexplained anemia or pancytopenia.

(but using for staging). Pancytopenia $\rightarrow$ Poor prognosis (late).

* The most compression symptom by L.N enlargement occurs in mediastinum over SVC (especially with non hodgkin).

- ★ Excisional biopsy with surrounding tissue is diagnostic for lymphoma.

How to approach with pt with lymphoma? (APL & Dx)

1. Staging
2. Determine it's type
3. Investigation to detect general health of pt.
(CBC, Hb, uric acid... etc)

- ★ Staging of lymphoma (Ann Arbor staging system of lymphoma (HL, NHL) :

Stage 1A or 1B → single lymphoid area or localized extra nodal site (stage 1E) ex-cervical L.N. only.

Stage 2A or 2B → 2 lymphoid areas or extra nodal sites on the same side of the diaphragm (either above or below diaphragm)

Stage 3A or 3B → lymphoid areas (including the spleen) on both sides of diaphragm.

Stage 4A or 4B → diffuse involvement of extra nodal organs (liver, bone marrow).

A: NO B-symptoms

B: $> 10\%$ wt loss, drenching night sweats, or unexplained fevers $> 38^{\circ}\text{C}$

E: involvement of a single extra nodal site contiguous or proximal to known nodal site. (extra nodal tissue)

Notes → Prognosis of lymphoma depends on it's stage + comorbidities (DM, RF... etc)

- * Staging of lymphoma can be detected by chest x-ray or CT chest, abdomen & pelvis or by PET scan (The most accurate). it's abbreviation of positron emission tomography & can also be used for follow up → if the malignant cells uptaked radiolabeled glucose, means they're still active & not respond to chemotherapy.
- * The response of Rx doesn't depend on size of L.N.
- * Any B stage is indicated for chemotherapy.
3A & 4A stages → indicated for chemotherapy
- * Treatment → ① Non pharmacological Rx (supportive + education + psychological support).
- ② Chemotherapy → All B stages, 3A & 4A.
- ③ Radiotherapy → For stage I & II (local L.N) → to limitate the complication of Rx.
- * Don't do radiotherapy for stage III & IV because they need high dose & lead to complications except bulky disease > 10cm & B-M invasion cases.
- * Start chemotherapy as early as possible with nodulosclerosis type because it's carry a good prognosis. (cure by 95%).
- * High grade non-Hodgkin lymphoma Rx by chemotherapy as early as possible & in low grade chemotherapy is used only for advanced stages III & IV
- * Chemotherapy cycles → Stage I & II → 2-6 wks
" III & IV → 6-12 wks with more intensive dose & more prolonged course.

• Chemotherapy regimes :-

Hodgkin $\rightarrow$ CHIVPP

Chlorambucil, Vinblastine, Procarbazine, Prednisolone).

Non-Hodgkin $\rightarrow$ L-CHOP

L-asparaginase, Cyclophosphamide, Hydroxydaunorubicin, Vincristine (Oncovin).

• Prognosis :- In general it's good.

Poor prognostic factors :-

Old age, coexist diseases, $\uparrow$ LDH level, $\uparrow$ B₂ microglobulin level, bulky disease, anemia or pancytopenia, wide metastasis (stage III or IV) with B symptoms.

• Note $\rightarrow$ Chlorambucil & Rituximab for resistant cases or given early for advanced cases.

• Palliative surgery may play a role when radiotherapy doesn't relieve compression symptoms.

• 2 Lymphoproliferative diseases lead to compression symptoms $\rightarrow$ are : 1) CLL, 2) Lymphoma.

Multiple Myeloma ...

Def:- Multiple myeloma is a malignant disorder of plasma cells characterized by :-

1. A monoclonal paraprotein in serum and/or urine.
2. Bone changes leading to pain and pathological features.
3. Excess plasma cells in the B.M 10%.

- **Epidemiology**:- Age: median age at Dx 70 yrs
Gender: more in males.
Race: more in black.
Mechanism $\rightarrow$ normal plasma cells in B.M $< 10\%$ $\rightarrow$ if $> 10\%$, one criteria going with multiple myeloma.
 - Plasma cell in blood invase B.M over long period of time $\rightarrow$ Pancytopenia.
 - malignant plasma cells release $\rightarrow$ Abnormal Antibodies (having light chain only) $\rightarrow$ paraprotein $\rightarrow$ $\downarrow$ severe in immunity.
 - Amyloid ppt deposit in Bone mainly, Heart & Kidney leading to osteolytic lesion in skull, hip & vertebrae.
restrictive cardiomyopathy & HF, nephrotic syndrome & RF.
(1st Amyloidosis) AL type.
 - Ca^{2+} replaced by paraprotein precipitation $\rightarrow$ $\uparrow \text{Ca}^{2+}$ in blood.
 - **Etiology and pathogenesis**:- The etiology is unknown.
The cell of origin is B-lymphoid cell.
 - **Clinical Features**:- Features resulting from plasma cell proliferation.
 - 1. **Skeletal involvement** $\rightarrow$ Bone pain, especially lower back pain is the most common Feature.
- D/D of old age + back pain:-
- ① Multiple myeloma
 - ② Metastasis From another ca.
 - ③ Infection
 - ④ Disk prolapse or herniation.
- $\uparrow$ with cough & sneezing. (ask about his job).

- Young male 30 yrs. old + Back pain → Ankylosing spondylitis
- Young Female - - + Back pain → Menstrual cycle
- Old Female + Back pain → Osteoporosis, especially
- Lower back pain + wt loss, Fever & night sweating
→ Pot's disease of T.B.

All these causes of back pain ↑ with movement except ankylosing spondylitis.

Back pain improve by leaning forward → Spinal stenosis

- Hypercalcemia a common complication results from bone destruction, it presents with thirst, polyuria, Polydipsia & constipation (calcium act as osmotic diuresis). hypercalcemia also lead to abdominal pain & Duodenal ulcer & mdd fluctuation (Abdominal groans & psychic moans).

- B.M infiltration → Features of B.M Failure (pancytopenia).

2. Features resulting from the para protein →

Infection → due to lack of normal immunoglobulin

Amyloidosis → may cause macroglossia, hepatosplenomegaly, celiac & renal.

Hyperviscosity (rare) IgG 70%, IgM 30% but

there's no features of hyperviscosity syndrome.

- ## 3. Renal Failure → occurs in 30% of pts. and is caused by hypercalcemia (hydronephrosis), recurrent infection (Pyelonephritis), deposition of para protein or light chains, ureic acid or amyloidosis → nephrotic syndrome.

Notes → Kidney is the most common organ affected by this disease.

because Failure occurs either by amyloidosis or pyelonephritis (2nd to recurrent infection) or by renal stone & hydronephrosis.

- 30% of multiple myeloma cases die from renal failure.
- Back pain + hypercalcaemia + renal impairment = Multiple myeloma.
- Pathological Fracture → spinal compression → paraplegia → numbness, tingling, weakness, urine incontinence.
Alarm symptom of back pain → urgent for MRI.
- Para proteins can lead to autonomic neuropathy → Postural hypotension, urine & stool incontinence without numbness & masking of hypoglycaemic attack.
- Investigation :- CBC → Pancytopenia
- ESR ↑↑↑↑ is often > 100 mm/hr.
High ESR not diagnostic, but normal ESR exclude the disease.

D/D → 1. Active T.B.

2. Multiple myeloma

3. Giant cell arthritis.

4. Infection.

Blood Film → Leukoerythroblastic picture may be present
B.M → shows > 10% plasma cells → Diagnostic but used only when diagnosis in doubt.

Lab → ↑ serum paraprotein (IgG in 70% or IgA) & Bence Jones protein (light chains) in urine.

Serum B₂-microglobulin ↑ (Poor prognosis).

Serum alkaline phosphatase usually normal, parathyroid level ~ normal, but serum calcium ↑.

These laboratory tests are diagnostic without need of B.M. examination.

Radiology → X-ray → Punched out osteolytic lesions.

CT scan or MRI shows lytic lesions typically in skull and axial & hip skeleton.

RFT → protein nephrotic range >3.5 g, disturbance of urea, Cr & electrolyte.

Treatment → Asymptomatic pt → no Rx, but if symptomatic

1. Supportive Rx + psychological Rx.

2. Chemotherapy → Thalidomide → chelating agent release para protein in urine or Melphalan + Prednisolone.

* Busulfan can be used, rare to cause lymphoma or leukemia.

3. Radiotherapy → For bone pain.

4. Autologous stem cell transplants → improve quality of life and prolong survival.

* Supportive care is:-

Allopurinol & Hydration to prevent hyperuricemia which may cause renal failure.

Hydration, steroid and bisphosphonate for hypercalcemia.

Plasma pheresis for hyperviscosity.

Waldenström's macroglobulinemia...

uncommon disease seen in older men, it's plasma cell malignancy characterized by the secretion of a monoclonal IgM protein.

characteristic feature:-

1. Monoclonal IgM paraproteinemia hyperviscosity syndromes are common ex: visual disturbance, DVT.
1. There is hepatosplenomegally & lymphadenopathy.

Disorders of Hemostasis...

Def:- Stop bleeding.

Hemostasis requires normal function of:-

1. Blood vessels [intact]
2. Platelets.
3. Clotting factors.

Note → Platelets & clotting factors could ↓ in quantity or quality (activity by X) & according to it's activity subdivided into mild, moderate & severe.

- Blood vessel defect as vasculitis → raised purpura, while platelets defect → flat purpura.

Endothelial continuation of bl- vs inhibit platelet aggregation & adhesion by PG.

when endothelial continuity losses → collagen release Thromboxane to stimulate platelet aggregation.



- Small blood vessels need platelets only for healing (Plug formation) in skin & mucous membrane.
- while large blood vessels need platelets + clotting factors.
- That's why platelet defect lead to internal & external hemorrhage & clotting factors defect lead to internal hemorrhage.

Note → Any patient presented with bleeding → ask about arthritis, joint swelling & deformity

Causes of bleeding regarding Bl. vs

Congenital

- Aneurysm.
- AV malformation.
- Sub arachnoid Hge.

Acquired

Vasculitis

Sterile

autoimmune

ANCA +ve

Septic

* Important notes in Hx of bleeding :-

① Site

② Amount & severity - spontaneous or after trauma?

③ O, C, D

④ Ask about complications: loss of conscious, symptoms of anemia, symptoms of shock & recurrent Bl. transfusion Hx.

⑤ Other sites of bleeding.

Systemic review → Respiratory renal syndromes, as - Wegner granulomatosis, goodpasture syndrome

ask about hemoptysis, hematuria, Bttx of Br. asthma

Causes of ↓ clotting factors

(↓ in number or in function)

Congenital

- Hemophilia

- Von Willebrand disease

Acquired

liver disease

Warfarine

heparin

Causes of ↓ Platelets

Thrombocytopenia

1. Anti-platelet

drugs as aspirin, platelet

2. Renal Failure

because ↑ urea (uremia)

lead to plt dysfunction.

3. Hypothermia

Congenital → Von Willebrand disease

Thrombocytopenia

B.M. Failure

- Aplastic anemia

- B.M. infiltration

by malignancy

- Metastasis from

solid tumors

- Amyloidosis $\left(\begin{smallmatrix} 1^\circ \\ 2^\circ \end{smallmatrix} \right)$

- Infection (T.B., HIV)

Immune suppressor drugs

↑ peripheral destruction

Intravascular

TTP

DIC

HUS

Hyperplenism (spleen)

Microangiopathic hemolytic anemia

• Here occurs on top of E. coli toxins → platelets aggregation + hemolysis + renal dysfunction (uremia) → anemia, thrombocytopenia, fever.

Antibiotics → CFI (↑ E. coli) toxins

Rx → supportive + plasma phoresis

- DIC caused by infection, burn, stress, trauma, surgery, M₃ leukemia $\rightarrow$ $\uparrow\uparrow$ clotting factor cascade & $\downarrow$ PLT depletion (coagulopathy & Hemorrhage) $\rightarrow$ Poor prognosis.
- D-Dimer & fibrinogen degradation product is very high in pt with DIC. also pt will have thrombocytopenia, Prolonged BT, PT & APTT time.

Laboratory and clinical Findings in Coagulation Disorders:

Disorder	aPTT	PT	BT	PLT count	Petechiae & purpura	Hemarthrosis
Hemophilia A, B, C	$\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	N	N	$\pm$	$\uparrow\uparrow$
Von Willebrand	$\uparrow\uparrow$	N	$\uparrow\uparrow\uparrow$	N	-	rare
Anti-Platelet	N	N	$\uparrow\uparrow$	N	$+$	$\pm$
Warfarin	$\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	N	N	$\pm$	$\uparrow\uparrow$
liver cirrhosis	$\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	N/ $\uparrow$	N/ $\downarrow$	$+$	$\uparrow\uparrow\uparrow$
heparin	$\uparrow\uparrow\uparrow$	$\uparrow$	N/ $\uparrow$	N/ $\downarrow$	$\uparrow\uparrow$	$+$
DIC	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow$	$\uparrow\uparrow$	$\downarrow\downarrow$	$+$	$+$

Notes $\rightarrow$ liver cirrhosis $\uparrow$ BT after splenomegaly & hypersplenism occur.

Heparin after administration by 2 months can induce thrombocytopenia (HIT) $\rightarrow$ heparin induced thrombocytopenia & it's 2 types $\rightarrow$ Type 1 after 2 wks $\rightarrow$ Platelets $> 100,000$ acute & reversible.

Type 2 occurs after prolonged administration $\rightarrow$ PLT $< 100,000$ irreversible.

Warfarine doesn't lead to thrombocytopenia except on top of HIT.

Rx of pt with HIT → oral new anticoagulant.

ex: apixaban, dabigatran.

Coagulation cascade

Intrinsic pathway

APTT

(inside B.V)

PLT thromboplastin

+ VWF

XII (12) → XII-a

XI (11) → XI-a

IX (9) → IX-a

VIII (8)

X (10) → X-a common pathway

Xa + Va (Ca²⁺)

Prothrombin (2) → Thrombin

Fibrinogen (1) → Fibrin → Clot Formation

XIII → XIII-a

(stabilized Fibrin)

Extrinsic pathway

PT or INR

(Disrupted B.V)

Tissue thromboplastin

VII (7) → VII-a



Notes → Warfarin work immediately once administered to the pt, but its effect occurs after 72 hrs, because active vit K need 72 hrs to deplete & stop its action.
Warfarin not given for acute thrombus because :-

1. has no immediate effect
2. ↓ Protein S & C in 1st hrs & leading to cutaneous ischemia & ↑ risk of thrombosis

Hemophilia :-

- Types :-
1. Hemophilia A is due to a deficiency of Factor VIII 8 (most common type)
 2. Hemophilia B (Christmas disease) due to a deficiency of Factor IX 9.
 3. Hemophilia C due to deficiency of Factor XI (rare)

Epidemiology :- Hemophilia A & B are x-linked recessive disorder. (Male affected, Female → carrier)

Hemophilia A & B have same clinical picture, but hemophilia B is less common and usually milder than hemophilia A
+ve FH but up to 30% have no Family Hx.

Clinical Features :-

Spontaneous bleeding, especially into joints (hemarthrosis) recurrent up to disability. & commonly in ankle & muscle

Onset in early childhood (ex: post circumcision) or 6 months after. (↑ risk of trauma) most common presentation

Increase risk of post operative or post traumatic hemorrhage

chronic debilitating joint disease caused by repeated bleeding.

Investigation:- CBC $\rightarrow$ anemia

Prolonged APTT.

BT, Prothrombin time, von willebrand factor level are normal.

Plasma Factor VIII activity & level $\rightarrow$ normally $> 50\%$

mild cases $\rightarrow < 25\% - > 5\%$

moderate cases $\rightarrow < 5\% - > 1\%$

Severe $\rightarrow < 1\%$

Treatment $\rightarrow$ Desmopressin (vasopressin analogue) help in synthesis of Factor 8 & vWF by endothelium of B.Vs.
use for $\rightarrow$ mild cases.

Rx of moderate & severe cases:-

1. Infusion of Factor 8 & there's 2 types:-

Natural $\rightarrow$ risky for infection.

Synthetic $\rightarrow$ risky for Antibody formation against it, so should given with immune suppression therapy.

CMV is the most infection persistant nowadays by blood transfusion & blood product transfusion.

2. VWF can be given alone.

3. FFP $\rightarrow$ but risky for infection.

4. Cryoprecipitate $\rightarrow$ 13, 1, 8, VWF.

It's not D.O.C in hemophilia B but can be effective with high dose.

5. Blood transfusion.

Von Willebrand disease (vWD)

Epidemiology :- The most common inherited bleeding disorder affecting 1% of population. (male & female can be affected).

Types of vWD :-

1. Type 1 : Partial deficiency of vWF (defect in quantity) **autosomal dominant**, most common.
2. Type 2 : Defect in vWF (defect in quality) **autosomal dominant**.

3. Type 3 : complete deficiency of vWF. **autosomal recessive** most severe & less common one.

• Pathophysiology and clinical presentation :-

The vWF is protein synthesized by **endothelial cells** & **megakaryocytes** & it has 2 functions :-

1. vWF adhesive link b/w platelets and the injured blood vessel wall → C/P include : immediate, mucocutaneous bleeding : skin bruising, epistaxis and menorrhagia (ex: platelet type). (Extrinsic).

2. vWF Functions carrier for Factor 8 → C/P of delayed deep tissue, post trauma (ex: coagulation type) (Intrinsic).

Diagnosis → ↓ von Willebrand Factor.

• **Investigation** : ↑↑ APTT + ↑↑ BT (↓ Factor 8 + ↓ Plt function). other test of platelet aggregation & PT time are normal.

CBC → anemia but Plt count → Normal unless there's mixed diseases.

• **Treatment** : 1. Desmopressin (↑ vWF) for mild cases.

2. Factor VIII / vWF concentrate in severe cases.

3. Cryoprecipitate or plasma contains VIII / vWF. **FFFP**.

Idiopathic thrombocytopenic purpura.

Def:- ITP is an immune mediated reduction in the platelet count. Antibodies IgG are directed against the glycoprotein IIb-IIIa or Ib complex. (may follow viral infection in child).

Presents in 2 Forms:

Acute ITP

Age: Children (2-9 yr).

Sex: both sexes.

Course: spontaneous remission.

Chronic ITP

20-40 yr, rare > 60.

Females. (F/M ratio 4:1)

Remission & exacerbation.

Clinical manifestations:-

Excessive bleeding caused by thrombocytopenia may be:-

- ✓ Mucosal (epistaxis, gingival, gastrointestinal bleeding or menorrhagia).
- ✓ Skin (purpura, petechiae & ecchymosis).
- ✓ Rarely cerebral hemorrhage may occur when the platelet count is $< 10,000$.

Note → A palpable spleen strongly indicate that ITP is not the etiology for the thrombocytopenia, because $< 3\%$ of pt. had an enlarged spleen "mild" → not detected clinically. That means splenomegally not exclude ITP.

Investigation:- CBC → $\downarrow$ PLT often $< 20,000$.

Do comb's test → if +ve → means there's associated AIHA
→ Evan's syndrome.

(Benign)

B.M → normal or $\uparrow$ numbers of megakaryocytes (this should be done before starting steroid because steroid can make change in B.M picture).

BT ↑↑.

PT & APTT → normal, Fibrinogen → normal

Antiplatelet antibodies (usually IgG)

* Treatment:-

1. Oral prednisolone (D.O.C) → 50% of pts respond (sensitive).

2. IV Immunoglobulin → causes temporary ↑ in plt count.

3. Splenectomy → if plt < 30,000 after 3 months of steroid therapy (steroid resistant). 70% of pts respond.

Note → Rituximab use nowadays to ↓ requirement of splenectomy.

4. Immunosuppressive therapy (ex: azathioprine, cyclosporine, cyclophosphamide, Anti-thymocyte globulin and vincristine may be used).

* Platelet transfusion: not recommended unless in life threatening condition. Plt < 20,000 - 30,000

Note → when pt undergo biopsy, surgery or after trauma Plt should be > 60,000.

in leukemic pt should be not less than 100,000.

Thrombotic thrombocytopenic purpura...

rare disorder characterized by microangiopathic hemolytic anemia, fever, thrombocytopenia, renal dysfunction (and/or hematuria) & neurologic dysfunction (Predominant) caused by Failure to cleave vWF from platelet.

• Treatment:- Prednisolone.

Plasma exchange in severe cases but, Plt transfusion is contraindication.

Blood transfusion...

It's transfusion of whole blood or blood product (ex: Packed RBCs, Plt, FFP, cryoprecipitate, albumin).

Pt should be under monitoring of vital signs → BP, Pulse, O₂Sa.

Side effects of blood transfusion:-

Some of them occur early within 24 hrs, & others occur late.

1. Minor febrile non hemolytic reactions (common, less likely if red cells are leucodepleted). leucodepleted means remove of WBC by radiation or by wash RBCs to relieve minor group antigen.

Note: 2. Febrile hemolytic reaction by ABO incompatibility.

characterized by intravascular hemolysis, hematuria, oliguria, febrile, dyspnea, hypotension & hypoxemia.

• Management of febrile hemolytic reaction:-

1. Stop blood transfusion.

2. Rematch (repeat cross match).

3. IV Fluid administration with central line (input & output chart with monitoring of vital signs).

4. Bronchodilator for wheezy chest.

chlorpheniramine → anti histamine

Doputamine → +ve inotropic

3. Severe allergic reactions (in pts with IgA deficiency).

4. Transfusion related lung injury (due to aggregation of neutrophils in lung capillaries) $\rightarrow$ change capillary alveolar blood barrier & change its permeability $\rightarrow$ $\uparrow$ alveolar edema (non cardiogenic). (ARDS).

How to differentiate b/w cardiogenic & non cardiogenic pulmonary edema?

(HF) (lung injury)

1. JVP $\rightarrow$ raised in cardiogenic.

2. Pulmonary B.P. in cardiogenic is more than 18 mmHg.

3. $\text{PaO}_2 : \text{FiO}_2$ ratio $\rightarrow$ if $< 200 \rightarrow$ ARDS.

5. Problems caused by massive transfusions ($\downarrow \text{Ca}^{2+}$, bleeding, $\uparrow \text{K}^+$).

Note $\rightarrow$ if pt have hyperkalemia but asymptomatic & there's no ECG changes $\rightarrow$ repeat K^+ test (pseudo $\uparrow \text{K}^+$).

6. Chronic iron over load 2^{nd} hemochromatosis (cardiac, liver, endocrine damage).

7. Infection (late) by HIV, hepatitis B, C, CMV, EBV, parovirus, malaria, syphilis, chagas disease, Lyme disease.

8. Prions (defective viruses) $\rightarrow$ spongy shaped brain front temporal $\rightarrow$ Variant Creutzfeldt-Jakob disease (vCJD) characterized by features of Alzheimer & convulsion.

9. Immune suppression [worsen prognosis of CA colon, and $\downarrow$ risk of rejection for renal transplant pt].

10. Graft versus Host disease (rare: lymphocytes from donor survive and attack the host).

- Massive blood transfusion $\rightarrow$ when pt receive blood equal or more than his blood volume within 24 hrs.
- Complication $\rightarrow$
 1. Hypothermia
 2. Hyperkalemia
 3. Hypocalcemia (due to citrate)
 4. Volume overload
 5. Bleeding tendency

Anticoagulant therapy

1. Warfarin (orally)

Reduced vit K promotes the carboxylation of glutamic acid which is important of factor 10, 9, 7, 2.

Warfarin inhibits vit K reductase enzyme. Full anti-coagulation occurs 72 hr after starting therapy.

Protein C & S levels also fall and this initially (first 2-3 days) lead to an increased risk of thrombosis and may lead to skin necrosis.

Control & monitoring by :- both PT & APTT are elevated but monitoring is doing by PT (INR) because it's more accurate (1st Factor affected is Factor VII (7)).

Treatment aim to maintain INR at level depending on indication ex $\rightarrow$ Mitral replacement 2.5 - 3.5

$\rightarrow$ Aortic replacement 2 - 3

$\rightarrow$ Mitral replacement + Atrial Fibrillation $\rightarrow$ 3 - 4

Note $\rightarrow$ Can be given for pregnant woman at 3rd trimester.

S/E $\rightarrow$ Hemorrhage, skin necrosis.

Management of warfarin toxicity :- $INR > 4$

* $INR > 4$, ask if there's bleeding

No

Yes

$INR 4-9$

$INR > 10$

- stop warfarin over 1 or 2 doses + vit K 2.5 mg orally.
- next day measure INR when reach therapeutic dose → Keep pt on 0.5 mg warfarin + lowest dose n.

- stop warfarin over doses + high dose of vit K (5mg) orally.
- when INR reach therapeutic value Keep pt on lowest dose of warfarin.

- stop warfarin
- vit K + FFP or Prothrombin complex concentrate (PCC) → very expensive.

* Causes of toxicity :-

1. Drug / Drug interaction (enzyme inhibitor → effect of warfarin).
2. Pt has dementia → over dose.
3. Vegetables → high with vit K.

Heparin...

Heparin is not absorbed orally so it's given subcutaneously or IV (in hospital).

Types:-

Unfractionated heparin (UFH)

- Activates anti-thrombin 3 → irreversible inactivates prothrombin Xa , Ixa and XIa . (9, 10, 11).
- short half life so given by IV infusion.
- More side effects
- Need monitoring by APTT.
- Eliminated by liver & Kidney.
- Protamine sulphate is antidote.

Low molecular weight

- Greater ability to inactivate Xa (10) and less effect on thrombin.
- Long half life so given once daily & subcutaneously.
- Same but less likely.
- Not necessary, but can be monitoring by Factor X (10).
- Eliminated by Kidney only (can act even 24 hr).
- NO antidote.

Note → LMW heparine used For malignancies that induce thrombosis because of long half-life.

- * Side effects:-
1. Hemorrhage.
 2. Osteoporosis.
 3. Thrombocytopenia.
 4. Allergic reaction.
 5. Hyperkalemia.